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AN EVALUATION OF DIETARY FACTORS IN THE TREATMENT  
OF LAENNEC'S CIRRHOSIS OF THE LIVER<sup>1</sup>

ARTHUR J. PATEK, JR., M.D.

*[Clinical Associate, Goldwater Memorial Hospital, New York, N. Y.]*

For over fifty years it has been believed that dietary factors might influence the course of liver disease, since the work of the liver is concerned with the metabolism of foodstuffs. Treatment has been aimed to lighten the burden of the injured organ and to provide those materials that might favor regeneration of liver tissue. What those factors might be has been more a matter of speculation than of fact. In Europe, a bland diet consisting chiefly of milk has been employed for a long time. In the light of present day knowledge this was a fairly good dietary program. It was also customary to prescribe saline purges and calomel to "relieve portal congestion"—a practice to be deplored.

In order to promote regeneration of liver tissue organotherapy was advocated as long ago as the 17th century. Liver was administered in the form of fresh pulp, dried powders, or extracts. Several articles on this subject have appeared in the French literature since 1900 (1, 2, and 3). Although the case reports are fragmentary there is a suggestion of beneficial results in certain instances.

In this country attention became directed to the glycogenic function of the liver. Interest was stimulated by the experimental work of Opie and Alford in 1915 (4), who showed that dietary factors can modify liver damage produced in the rat by chloroform and phosphorus. A diet of oats and sugar appeared to give more protection than one consisting entirely of meat or fat. Later studies by Mann and Magath (5) demonstrated that hepatectomized dogs could be revived from coma by the administration of glucose. The conclusions reached in these studies doubtless were justified under the conditions of the experiments. However it is unfortunate that their conclusions were applied by others to the treatment of Laennec's cirrhosis, in which the conditions are not the same. It also is curious that little note was taken of the experiments reported in 1919 by Davis and Whipple (6), who showed that protein was protective against chloroform poisoning in the dog.

The idea that dietary factors might play a role in the etiology of cirrhosis was suggested by observers in the Orient and Near East (7, 8, 9, and 10), where alcoholism was not a feature of the disease. It was noted that cirrhosis was prone to occur in persons who had been on deficient diets. Although these observers stressed the frequency of malnutrition in the background of liver cirrhosis, other

<sup>1</sup>From the Research Service, 1st Division, Goldwater Memorial Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York.

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factors such as malaria, dysentery and parasitic infestations were considered to be of primary etiologic importance. So far as I know, a systematic attempt to influence the course of the disease by specific diets was not made.

Earlier studies on pellagra (11) and polyneuritis (12) in this country indicated that the "alcoholic" forms did not differ essentially from the endemic forms of these diseases. Since patients with alcoholic cirrhosis of the liver frequently show signs of dietary deficiency, particularly of factors in the vitamin B complex, it was postulated that an analogy might exist between the occurrence of cirrhosis and these deficiency diseases. Therapeutic trial therefore was made of a nutritious diet, rich in protein and supplemented with vitamin B complex. Several reports have been made during the course of this study (13-16). At the risk of being repetitious, I shall describe briefly our experience with this program:—

In the past 10 years 124 patients with cirrhosis of the liver (in failure) have been treated at the Research Service, First Division, of the Goldwater Memorial Hospital. They were fed a highly nutritious diet, supplemented with Brewer's yeast and intramuscular injections of liver extract and thiamin chloride. The diet consisted of meat and dairy foods, fruit, and green vegetables. Meat was served twice daily and milk 5 times daily—3 times with meals and twice in the form of milk nogs containing the yeast powder.<sup>2</sup> It was impressed upon the dietetic, nursing, and medical staffs that the diet was the chief medication. Account was taken of the food intake of the patients. In order to obtain optimal results it was often necessary to individualize the diets according to the patient's food habits and tastes. On analysis the average diet contained carbohydrate 365 gms., protein 139 gms., fat 175 gms., (calories 3591). During the period of rapid ascites formation the intake of fluids was limited to 2500 cc. daily and salt was moderately restricted. Ammonium chloride in enteric-coated tablets (4-6 gms. daily) and mercupurin or mercuhydrin (2 cc. twice weekly i.m.) have been given in order to lengthen the intervals between abdominal paracenteses.

The patients have done well on this regimen, if one compares their course with earlier experience in this disease. All had shown signs of severe liver failure on entry to the hospital. After varying periods of time 51 showed signs of clinical improvement, evidenced by the loss of ascites, jaundice, and edema, by significant gain in weight and strength, and by improvement in tests for liver function. It generally required at least 2 months of treatment before significant changes appeared. Comparison was made with a series of 386 hospitalized patients with liver cirrhosis who entered 5 New York hospitals during the years 1920 to 1930. These latter patients received either no specific dietary care or they received the high carbohydrate, low protein diet which was standard treatment at the time. Although the control series was not ideal it provided a base line for comparison.

<sup>2</sup> A detailed scheme of the dietary schedule is presented in an earlier paper (14). There is an art in the administration of Brewer's yeast. Some prefer to mix it with tomato juice. We have given it in milk, beginning with 10 gms. twice daily to the glass, increasing gradually until 25 gms. twice daily are tolerated. Sugar and vanilla are added for flavor. For those who have persistent intolerance to yeast, an oral crude extract has been substituted. The preparations employed were Lederle's Oral B Complex or Wyeth's B-Plex, one ounce twice daily.

The duration of life after the onset of ascites was determined in these two groups of cases. Ascites was present in 230 cases of the control series and in 115 of the treated series. Thus at the end of one year 40 per cent of the controls were alive in contrast to 65 per cent of the treated series; at the end of two years 20 per cent of the controls and 50 per cent of the treated series; at the end of five years 7 per cent of the controls and 30 per cent of the treated series were alive. The differences appear to be significant.

Biopsy of the liver has been performed in about 50 cases during the course of therapy. The evidence for histological improvement associated with clinical improvement has been unimpressive. There may be vast structural derangement for years after clinical improvement has occurred. This is not surprising, since one frequently encounters such changes in the livers of patients whose cirrhosis has been latent throughout life. However there is ample evidence of functional improvement, and the thought is inescapable that something has altered the course of the disease. From these data one may not attribute the beneficial effects to protein, to vitamin B complex, or to any other specific dietary factor. One may infer only that these patients have improved after treatment with a highly nutritious diet and adequate nursing care. Similar plans of treatment have been carried out in other clinics (17-20). In general the reports have been favorable. More recently certain specific dietary factors have been advocated for the treatment of cirrhosis.

What is the basis for the use of specific dietary factors in the treatment of this disease? This stems from a series of experimental studies carried on in different laboratories in this country during the past 7 years (21-28), and more recently in Great Britain (29, 30). (I refer especially to the excellent work of Blumberg, Chaikoff, Goldschmidt, György, Rich, Sebrell, Webster, Whipple, and their associates.)

These studies demonstrated (a) that necrosis and cirrhosis of the liver can be produced in the experimental animal by dietary deficiency alone, (b) that dietary factors modify the degree of liver injury produced by hepatotoxins such as chloroform and arsenic. In general it is agreed that protein is the chief protective dietary component for the liver, whereas high fat intake may exert a deleterious effect upon the damaged liver. It also has been shown that protein may be protective chiefly because of the amino acid methionine or its biological equivalent choline and cystine, since these substances (added to a low protein diet) prevent the development of experimental cirrhosis. Best (31) and his associates previously had shown the lipotropic action of these protective substances.

On the basis of the experimental studies, several writers have suggested that patients with cirrhosis be fed diets rich in protein, poor in fat, and supplemented with methionine or choline and cystine. A number of reports have described favorable effects from these dietary supplements upon the course of the disease. More recently intravenous liver extract has been suggested as an adjuvant to the dietary program. Although an appraisal of these newer measures may be premature, it is well to examine the data at hand. Two questions present themselves: First, what is the rationale for the use of a particular substance; Second, what is the evidence for a specific effect.

*Protein.* There is ample rationale for the use of protein foods. The tissue wasting and low serum proteins seen in cirrhosis indicate depletion of protein stores. It is logical to feed proteins to stimulate regeneration of plasma and tissue proteins. According to the experimental evidence, protein should help prevent further liver damage. Whether restoration of liver tissue depends solely upon the feeding of protein is not yet established.

The experiments of Bollman (32) have been cited in the past as evidence against the use of proteins in the treatment of cirrhosis. In studies on carbon tetrachloride cirrhosis in dogs, the animals tolerated a "balanced" diet or high carbohydrate diet better than one composed of lean meat alone. It is difficult to reconcile these observations with clinical studies. It is possible that carbon tetrachloride cirrhosis in the dog differs from human cirrhosis. It also is possible that protein per se was not harmful and that toxic factors were present in the lean meat. In any case, the author did not intend that protein should be excluded from the diet because of these experimnts.

*Carbohydrate.* On the basis of earlier experiments (4, 5) a diet very rich in carbohydrate was popularly employed. However, results with this treatment were disappointing. This could be explained in the light of later work. A diet excessively high in one component would be relatively low in the others,—protein and fat. The diet probably was ineffectual not because of its carbohydrate content but because of its lack of protein and fat and its unpalatability. This fact often has been ignored in both experimental and clinical studies, namely that excess of one factor creates a relative deficiency of others.

There is rationale for the use of carbohydrate foods in the treatment of cirrhosis on two accounts: (1) to provide the caloric needs, (2) to serve as a protein-sparer, since in the absence of carbohydrate, protein is utilized to supply the caloric needs. There also is clinical evidence for its use especially in cases of subacute hepatitis (33) and in cholemia (34), in which dramatic effects are sometimes seen after the intravenous administration of glucose.

*Fat.* Most writers have advised fat-poor diets for patients with liver disease. Experimental evidence is based upon observations that excess dietary fat predisposes to liver injury, that fatty livers are associated with liver injury, and that lipotropic substances prevent these fatty changes. However, it should be pointed out that animals placed on very high fat diets seldom eat much food. Such diets usually are associated with starvation and protein deficiency as well. In the presence of adequate protein, the fat content of experimental diets has been of little consequence.

Clinical evidence is based largely on experience with obstructive jaundice, in which fat restriction is reasonable because of decreased bile flow and faulty digestion. The "case against fat" in the treatment of liver cirrhosis, I believe, is less valid. In practice we have seen no ill effects from the use of diets containing 175 gms. of fat. The stools are not fatty. Liver biopsies made during treatment with these diets do not show fatty changes. If one restricts fat severely, then cream, butter, eggs and other nutritious foods are curtailed, and



the appetite falls off. The present evidence, it would seem, does not justify severe restriction of fat.

*Choline and Methionine.* The importance of choline or methionine in the prevention of experimental nutritional cirrhosis is well established. In experiments designed to test the curative effects of these substances the evidence is less conclusive. In the reports (25, 35) on this subject animals that have shown signs of recovery with choline or methionine therapy also have shown a tendency to gain weight in excess of the control animals. This implies either a greater food intake or a more efficient utilization of nutrients, or both. Under these conditions it is difficult to divorce the effect of food intake from the effect of the adjuvant. Although methionine and choline prevent the development of cirrhosis it does not necessarily follow that they alone promote repair and regeneration of liver tissue once the damage has occurred. Further work doubtless will clarify this subject.

For similar reasons it is difficult to interpret clinical reports (36-41) which ascribe beneficial results to the use of these substances. In certain studies patients received a high caloric, protein-rich diet with supplements of yeast, liver, or synthetic vitamins for a "control" period usually of weeks, occasionally of a few months. If there was no apparent improvement at the end of this period choline or methionine was added. Since there is much variability in the time response of patients to the dietary treatment alone, it is hazardous to interpret these data.

In other studies "control" patients received a high caloric protein-rich diet with or without supplements of yeast, liver, and synthetic vitamins. Test subjects were fed a similar diet with added choline or methionine. A greater survival period in the latter group was attributed to the use of these drugs. The series of cases are too small and the differences not sufficiently great, I believe, to be of significance.

In other words, to determine whether any substance is specifically effective the conditions must be subjected to more rigid controls than have been employed thus far. The effects of bed rest, basal diet, and caloric intake must be established. The criteria for improvement must be defined. This is easier said than done. There are difficult problems in devising a so-called basal diet, in obtaining parallel cases with comparable degrees of liver failure, and in defining criteria or standards for measuring improvement.

Our own experience with the use of choline and methionine has been limited to 6 patients who failed to respond adequately to the dietary treatment previously described. In all instances they had reached a "plateau" for from 6 months to 3 years, showing neither progressive failure nor improvement. The addition of choline or methionine to their diet was followed by no significant changes.

The rationale for the use of methionine or choline in cirrhosis of the liver is not clear-cut. The field of promise would seem to be in the pre-cirrhotic, fatty stage of the disease. There are no harmful effects from these substances, but

there may be harm in relying upon them to the extent that other dietary factors are neglected.

*Other Measures.* The preliminary reports of Ralli, Hoagland (42), and their associates with the use of intravenous liver extract appear promising. Relatively large amounts of the material can be given intravenously when compared to the intramuscular route. Although our experience has been limited to a small series, we have been impressed by the sense of well being and sharp gain in appetite enjoyed by patients receiving intravenous liver extract.

The intravenous administration of concentrated serum albumin solution appears to favor diuresis and the loss of ascites in certain patients (43, 44) whereas it has been relatively ineffectual in others (45, 46). The place of these newer measures in the treatment of cirrhosis of the liver awaits further trial.

#### CONCLUSION

Laennec's Cirrhosis of the liver formerly was thought to be a progressive disease, with a relentless downhill course. This concept no longer is tenable. A significant number of patients with severe liver failure and a much larger percentage of patients with moderate liver damage can recover with dietary treatment.

With early diagnosis and early institution of appropriate therapy the prognosis of this disease should become more favorable.

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SHOCK, HEMORRHAGE AND PULMONARY EMBOLISM AS FACTORS IN  
ITS PRODUCTION\*

A. M. MASTER, M.D.; S. DACK, M.D.; A. GRISHMAN, M.D.; L. E. FIELD, M.D.  
AND H. HORN, M.D.

During the past decade considerable progress has been made in the study of acute coronary artery disease and myocardial infarction, but not until recently has it been generally recognized that myocardial necrosis or infarction may occur in the absence of acute coronary occlusion (1-6). This type of acute myocardial disease we have termed "acute coronary insufficiency" (myocardial infarction without acute coronary occlusion).

Acute coronary insufficiency is a deficiency of the coronary circulation due to discrepancy in the demands of the myocardium and its available oxygen or blood supply. The term acute coronary insufficiency should not be construed to include acute thrombotic occlusion of the coronary artery; it is used solely to indicate dysfunctional insufficiency of coronary flow, which is usually transient and reversible although its effect on the myocardium may be permanent. For the sake of custom and convenience the term angina pectoris is retained to indicate a very transient episode of acute coronary insufficiency characterized by substernal or precordial pain. Acute coronary occlusion is a disease entity characterized by sudden, complete, irreversible occlusion by thrombosis or by intimal hematoma of the coronary lumen. There is always underlying coronary arteriosclerosis.

We pointed out in earlier publications (5, 6) that the distinctive anatomical and electrocardiographic features of acute coronary insufficiency permit its differentiation from acute coronary artery occlusion with massive myocardial infarction. More recently (7, 8) it has become clear that acute coronary insufficiency possesses not only a distinct pathological physiology, definite predisposing factors and a characteristic electrocardiographic pattern but also demands definitive therapeutic measures. It is thus a complete clinical entity (7, 8). In this paper, therefore, we shall summarize the physiological considerations, precipitating causes, anatomical and electrocardiographic patterns, clinical features, prevention and therapy of acute coronary insufficiency. Whereas it is well recognized that active treatment in acute coronary artery occlusion is of value mainly in management of the complications which may arise, we have learned that acute coronary insufficiency may be treated directly, specifically, and effectually.

In acute coronary artery insufficiency, myocardial ischemia results from a disproportion between the oxygen requirements of the myocardium and the coronary blood flow and is provoked by factors which increase the work of the heart or decrease coronary blood flow. When the myocardial ischemia is severe or

\* From the Electrocardiographic Department of The Mount Sinai Hospital, New York.

protracted, myocardial necrosis or infarction may develop without acute coronary occlusion. The factors precipitating acute coronary insufficiency fall into three groups: (1) *Sudden increase in cardiac work* through increase in blood pressure, heart rate, or cardiac output. Although the coronary blood flow may be simultaneously augmented, the increase may be insufficient to meet the excessive nutritional demand of the heart, thereby creating a relative inadequacy of coronary blood flow. This condition may occur following severe physical exertion, emotional stress, tachycardia, hypertensive crisis, acute thyroid crisis, acute infectious states, or drugs such as adrenalin and pituitrin. (2) *Diminution of coronary blood flow* by means of suddenly lowered blood pressure and diminished cardiac output. This condition is observed following shock and peripheral collapse due to any cause, hemorrhage, acute hypotensive states, extreme bradycardia, heart failure, diminished circulating blood volume, and acute abdominal catastrophes. An absolute deficiency of coronary blood flow exists. (3) *Interference with oxygenation of the blood*, with resultant impairment of its oxygen-carrying power. Myocardial anoxia may result from generalized anoxia, e.g., asphyxia, general anesthesia, carbon monoxide poisoning, acute anemia, recurrent pulmonary embolism, acute pulmonary diseases, and bronchial asthma. In these states, despite the compensatory increase in coronary blood flow, the diminished arterial oxygen saturation is inadequate to meet the nutritional demands of the heart. A combination of the three types of causative factors inducing acute coronary insufficiency frequently occurs.

#### PATHOLOGICAL ASPECTS

The degree and extent of the myocardial changes (4, 5) that take place in acute coronary insufficiency vary with the duration and severity of the precipitating and predisposing factors. The gross picture is characteristic and usually consists of small, focal disseminated areas of tawny, mottled or hemorrhagic subendocardial discoloration in the left ventricle. Occasionally lesions simulating fatty infiltration are observed. The changes may occur in any portion of the ventricle, but they are generally most evident in the papillary muscles, especially the posterior, and in the left posterior wall and the left ventricular aspect of the septum. Focal infarction of the right ventricle occurs but it is relatively uncommon. In mild cases, the changes may be discovered only on histological examination. In severe cases, the lesion may be noted as large focal or confluent areas of myomalacia, involving almost any portion of the left ventricle, but confined to the subendocardial zone.

Pericarditis has never been observed in acute coronary insufficiency. Mural thrombi have been seen rarely, and where found were ascribed to pre-existing cardiac disease. In a few cases the recent myocardial changes were confined entirely to the papillary muscles of the left ventricle.

Careful and detailed search failed to reveal recent occlusion of a coronary artery in any of the cases examined. Arteriosclerosis of the coronary arteries, however, was commonly found with mild to severe narrowing of the lumen. Other structural abnormalities which contributed to decreased flow of coronary



blood included aortic valvular lesions and arteriosclerotic or syphilitic osteal stenosis. In the absence of predisposing anatomical changes, severe shock, anoxemia, or massive gastrointestinal hemorrhage were found to underlie production of myocardial necrosis. In view of these observations, we must conclude that acute coronary insufficiency with myocardial necrosis may occur even when the coronary arteries are normal, if myocardial ischemia or anoxia is sufficiently severe or protracted.

Localization of the myocardial lesions in the subendocardial region and the papillary muscles, more particularly in the posterior papillary muscle, is believed to be due to the fact that these areas are remote from the source of blood supply. Moreover, since the subendocardial layer and the papillary muscles are rich in capillary and precapillary anastomoses, they require an abundant blood supply. It follows that anoxia, either of the anemic or the stagnant type, is more readily manifested in these areas than in others.

Another factor that contributes to the localization of pathological changes in the subendocardium and the papillary muscles is a purely mechanical one, dependent on the gradient in intra-myocardial pressure. During the height of systole this pressure diminishes from the deeper to the more superficial layers. In the depth of the myocardium, the intra-myocardial pressure is greater than the aortic pressure, whereas in the superficial layers, it may be equal to or even less than the pressure in the aorta and the coronary arteries. During isometric contraction increased pressure is exerted against the susceptible regions. Moreover, the papillary muscles perform comparatively more work than do other portions of the myocardium. It is probable, therefore, that these areas demand a greater oxygen supply, and consequently react more readily to oxygen deprivation.

#### THE ELECTROCARDIOGRAM

The differences in character and location of the infarctions in acute coronary insufficiency and in acute coronary occlusion are reflected in the distinctive electrocardiographic patterns of the two conditions (5). The electrocardiogram of acute coronary insufficiency discloses depression of the S-T interval and flattening or inversion of the T-wave in two or more leads. Except in rare instances, elevation of the S-T segment and deep Q-waves, so characteristic of acute coronary occlusion, do not occur in acute coronary insufficiency. Each of the leads is affected with equal frequency, and not uncommonly the S-T depression and abnormal T-wave are observed in the four leads simultaneously.

The maximal changes usually occur in the first record obtained and the changes may regress in serial records if the coronary insufficiency is ameliorated. Duration of the changes depends on the severity of the myocardial ischemia; they are often transitory if the factor precipitating the ischemia is rapidly abolished. For instance, if the precipitating factor is hemorrhage and shock the electrocardiogram may return to normal soon after a blood transfusion is given. Electrocardiographic alterations of relatively short duration usually indicate reversible anoxic or ischemic changes, and not anatomical myocardial lesions.

Longer lasting electrocardiographic abnormalities denote subendocardial infarction of varying degrees of severity.

By means of anoxemia or exercise tests, an electrocardiogram typical of acute coronary insufficiency can be obtained in patients with coronary arteriosclerosis. For example, an electrocardiogram made after the standard 2 step exercise (9) and the 10 per cent anoxemia (13) test reveals S-T depression with or without T-wave inversion in one or more leads. These transient alterations disappear either a few minutes after cessation of exercise or with inhalation of pure oxygen. These tests have now been standardized for routine application in patients who are suspected of having coronary artery disease and a positive result is fairly conclusive evidence of deficient coronary blood flow.

#### CLINICAL ASPECTS

The simplest and most common clinical expression of acute coronary insufficiency is angina pectoris. This is a transient episode of coronary insufficiency, initiated by effort, emotion, or other factor which increases the work of the heart in the presence of pre-existing coronary arteriosclerosis. Ischemia of the myocardium results from inability of the arteriosclerotic coronary vessels to permit an adequate supply of blood to reach the myocardium during the increased work. This condition is manifested clinically by substernal pain which is commonly transitory and relieved by rest or vasodilators. An electrocardiogram obtained during the paroxysm of pain often discloses evidence of acute coronary insufficiency; that is, transient S-T depression and T-wave inversion. The findings during spontaneous angina pectoris are similar to those observed in patients with coronary disease who have been given the exercise or the anoxemia tests.

In the more severe type of acute coronary insufficiency the clinical picture may simulate that of acute coronary occlusion. Chest pain occurring during rest as well as after effort, shock, impaired heart sounds, drop in blood pressure, fever, leukocytosis, and rapid sedimentation rate may be noted. The severity of clinical symptoms depends on the degree of myocardial ischemia and the extent of the infarction. As a rule, the clinical signs are not as marked as they are in acute coronary occlusion, and on occasion, they may be entirely absent. For diagnostic purposes an electrocardiogram typical of coronary insufficiency together with the presence of one of the precipitating factors should make it possible to differentiate acute coronary insufficiency from coronary artery occlusion.

As we have already pointed out, the principal causes initiating acute coronary insufficiency are increasing cardiac work, diminution in coronary blood flow, and interference with oxygenation of the blood. For adequate prevention and management of acute coronary insufficiency, it is essential that the precipitating agents be recognized by surgeons as well as by internists. Shock, hemorrhage, and pulmonary embolism—three of the most important of the precipitating factors—will be discussed in detail.

*Acute coronary insufficiency due to shock.* Coronary insufficiency is a common complication of shock, particularly in patients of the older age groups who have pre-existing coronary artery disease. There are several physiological mecha-



nisms in shock which lead to coronary insufficiency. The circulatory dynamics in shock (12, 13) are characterized by diminution in circulating blood volume and in venous return to the heart with subsequent diminished cardiac output and fall in arterial blood pressure. Since the coronary blood flow is dependent on cardiac output and on arterial blood pressure, it is apparent that shock results in absolute diminution of coronary blood flow. The blood pressure may be temporarily maintained by compensatory peripheral arteriolar vasoconstriction, but it will invariably fall as the shock progresses unless this sequence can be halted at the onset. Experimental evidence suggests the possibility that peripheral vasoconstriction leads not only to visceral ischemia, but to venous stasis, particularly in the splanchnic area, thereby contributing to diminution in circulating blood volume. Another compensatory mechanism in shock is found in acceleration of cardiac rate. The tachycardia is an attempt to compensate for decreased stroke volume. These abnormalities of circulatory dynamics may result in acute coronary insufficiency and so in myocardial ischemia and anoxia. The diminution in coronary blood flow, if of sufficient degree to produce myocardial impairment, may also diminish the cardiac output and lower the blood pressure. The vicious cycle which is developed leads to a state of irreversible shock. In the presence of coronary sclerosis, cardiac hypertrophy, heart failure, and aortic stenosis, diminished coronary blood flow caused by shock will be superimposed on an already inadequate circulation. When the myocardial ischemia is severe and prolonged, subendocardial infarction results.

We have observed acute coronary insufficiency following shock due to surgical procedures, trauma, acute hemorrhage, and spinal anesthesia. Other precipitating factors were pulmonary embolism; acute abdominal conditions, such as a ruptured viscus or acute peritonitis; acute infections; hypoglycemic shock; hypertensive crises; and hypotensive states such as occur in Addison's disease and following thoracolumbar sympathectomy. Tachycardia, fall in blood pressure, gallop rhythm, impaired heart sounds, and even acute congestive heart failure have been observed as manifestations of acute coronary insufficiency during and following shock. The correct clinical diagnosis can be established by proper evaluation of the precipitating factors and by the presence of RS-T depressions and T-wave inversions in the electrocardiogram (fig. 1).

*Acute coronary insufficiency due to acute hemorrhage.* Acute hemorrhage (5, 11) is almost as frequent a precipitating cause of acute coronary insufficiency as is medical and surgical shock. In view of its profound effects on the general and coronary circulation, the occurrence of hemorrhage in a patient with known coronary artery disease or in an elderly individual deserves the close attention of gastro-enterologists and surgeons as well as of internists and cardiologists, more especially, since acute coronary insufficiency resulting from hemorrhage responds readily to proper treatment.

Following acute blood loss from bleeding peptic ulcer, esophageal varices or other source of moderate or severe hemorrhage, the vasomotor compensatory mechanism may be unable to maintain the normal hemodynamics and shock will ensue (12, 13, 14). As in other types of shock, diminished circulating blood

volume and cardiac output, lowered blood pressure, tachycardia and decreased aortic perfusion or "head-on" pressure, contribute to diminution of coronary blood flow. In addition, hemodilution and anemia secondary to blood loss further impair the nutritional supply of the myocardium since the oxygen-carrying capacity of the blood is reduced. Profound alterations in visceral

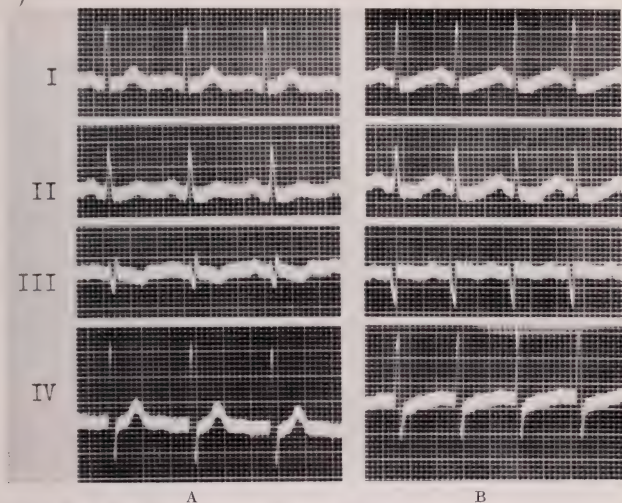


FIG. 1. M. G. (Adm. #462762) Acute coronary insufficiency due to postoperative shock in a white male, age 59 with carcinoma of sigmoid. B.P. 80/60, hemoglobin 90 per cent. Death due to shock on 5th postoperative day 9/30/40. Postmortem findings—moderate left ventricular hypertrophy, pulmonary edema and coronary arteriosclerosis with moderate narrowing. Microscopically early ischemic changes were noted in the myocardium, a result of the acute coronary insufficiency.

A. Preoperative ECG (9/20/40) is essentially normal. B. Postoperative ECG (9/28/40) shows sinus tachycardia, RS-T depression and diphasic T waves in leads I, II and IV: these were manifestations of the acute coronary insufficiency and myocardial ischemia precipitated by the shock.

metabolism and humoral composition may accompany hemorrhagic shock. All these factors operate to bring about a severe deficiency in the quantity and quality of the coronary circulation, which may be followed by myocardial ischemia and necrosis.

Anemia resulting from hemorrhage is not in itself a predominant factor in the pathogenesis of acute coronary insufficiency, although it plays a significant contributory part. Chronic anemia alone, even of long standing, is not likely to produce coronary insufficiency, since the compensatory mechanism of increased cardiac output and speeded circulation usually acts to maintain normal myocar-

dial nutrition. In acute hemorrhage, on the other hand, the circulatory sequelae may be severe, even when the blood hemoglobin is not appreciably lowered. Although coronary insufficiency is generally more marked when the acute anemia is profound, the decreased blood volume resulting from the hemorrhage is regarded as the major mechanism.

Experimentally, evidence that coronary insufficiency and myocardial ischemia followed severe or repeated bleeding of animals, was manifested by characteristic electrocardiographic findings and focal necrosis in the myocardium (15-17). In the early stages, infusions of whole blood, plasma, or serum were equally effectual in eliminating evidences of acute coronary insufficiency, a finding that lends support to the contention that decreased blood volume is fundamentally responsible for the insufficiency.

A number of clinical reports (5, 11, 18-20) stressed the relationship of acute hemorrhage to angina pectoris, heart failure, and development of acute RS-T and T-wave changes in the electrocardiogram. Actual myocardial necrosis or infarction was also observed in such cases. Scherf, Reinstein, and Klotz (21) reported 15 cases of profuse gastric hemorrhage with RS-T and T-wave changes in 14 of the patients. These authors ascribed such alterations to myocardial anoxia incident to reflex coronary spasm accompanying the generalized vasoconstriction in hemorrhage.

In our study of 103 cases of moderate and severe hemorrhage in which one or more electrocardiograms were obtained during the stage of active bleeding, it was found that in the great majority the source of hemorrhage was in the gastrointestinal tract. Bleeding peptic ulcer was the leading cause; esophageal varices, ulcerative colitis, and hemorrhoids accounted for the remainder.

Fifty-nine patients presented signs of acute coronary insufficiency. In 6 of these patients clinical signs, such as precordial pain and heart failure, occurred without electrocardiographic abnormality; in 34 patients typical electrocardiographic changes occurred in the absence of clinical signs of acute coronary insufficiency; in the remaining 19 patients, both clinical and electrocardiographic signs were present (fig. 2).

Twenty-two of the 103 patients died, in most cases from the exsanguinating effects of the hemorrhage; 18 of these showed evidence of acute coronary insufficiency prior to death. Anatomical evidence of acute coronary insufficiency was found in four of the 15 autopsied cases (fig. 3); these changes consisted of focal disseminated subendocardial necrosis. In one of these patients, a 19 year old girl with ulcerative colitis, whose heart was otherwise normal, death was due to exsanguinating hemorrhage. The other three patients presented evidence of pre-existing coronary arteriosclerosis, and one of these had, in addition, aortic stenosis. Acute coronary artery occlusion was not found in any instance.

The precipitating factors responsible for the acute coronary insufficiency were analyzed. These were in order of their frequency the degree of shock, drop in blood pressure, tachycardia, and decrease in hemoglobin level. These factors were more frequent and more marked in the group which revealed acute coronary

insufficiency clinically by electrocardiogram and by pathological change in the myocardium at autopsy.

It is our impression that shock and its associated hemodynamic abnormalities were the most significant contributing factor in these myocardial alterations. Clinical manifestations of shock were not, however, invariably present in patients who developed signs of coronary insufficiency. In the latter anemia may have played a major role. In another group, particularly in the postoperative and

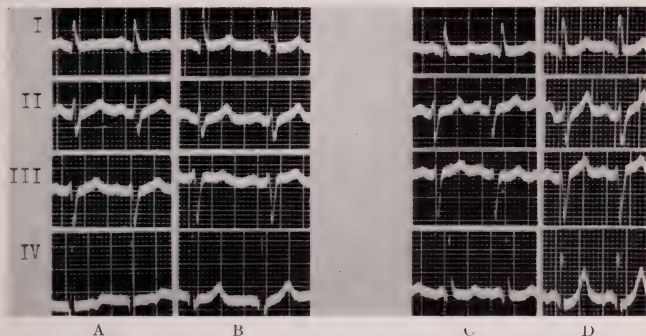


FIG. 2. S. S. (Adm. #544236) Acute coronary insufficiency due to hemorrhage in a male age 60. The patient was observed in two bouts of severe hematemesis from a chronic peptic ulcer. During the first episode (9/10/45) he developed shock, B. P. 80/40, pulse rate 120, hemoglobin 30 per cent, poor heart sounds. ECG on 9/11/45 (A) shows semi-inverted T1 and T4 which return to normal on 9/18/45 (B) following several transfusions. In the second bout of hemorrhage (1/17/46) there was shock, BP 90/50, tachycardia, hemoglobin 23 per cent. ECG on 1/21/46 (C) shows slight RS-T depression in leads I and IV and low T1. ECG on 1/26/46 (D) shows marked tachycardia and RS-T4 depression, suggestive of acute coronary insufficiency. On 1/26 the patient developed severe precordial pain, dyspnea, shock, and died within several hours. At autopsy there were scattered focal areas in the myocardium which revealed loss of striations, homogenization, focal myonecrosis, nuclear pyknosis and reactive infiltration with polymorphonuclear leucocytes. These areas were located mainly in the subendocardial regions of the posterior wall and the papillary muscles of the left ventricle. The coronary arteries were widely patent and showed minimal arteriosclerosis.

ulcerative colitis cases, dehydration, inanition, sepsis, and toxemia were believed to be important contributing factors.

The electrocardiograms were characteristic of acute coronary insufficiency in 53 of the 103 patients. Most of these showed depression of the S-T interval with or without inversion of the T-wave in one or more leads (fig. 2). S-T elevations and deep Q waves were rare. The characteristic signs of myocardial infarction due to acute coronary occlusion were not observed in any of the tracings. The electrocardiographic pattern of coronary insufficiency generally developed during the stage of active bleeding, when shock and changes in blood pressure, heart rate and hemoglobin level were at their maximum. The abnormalities were for the



most part transient, disappearing within a few days following therapeutic intervention. In a few cases, on the other hand, the electrocardiographic abnormalities persisted for a period of several weeks and were accompanied by findings suggestive of myocardial infarction; namely, fever, leucocytosis, and an accelerated sedimentation rate.

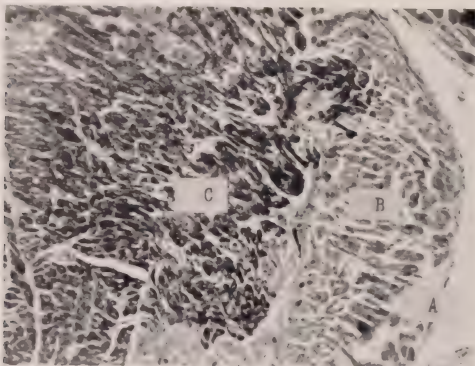


FIG. 3. H. S. (Adm. #471642) Acute coronary insufficiency with subendocardial infarction due to hemorrhage and aortic stenosis. A 67 year old female who since 1940 experienced seizures of angina pectoris, precipitated by repeated bouts of gastro-intestinal hemorrhage, during which hemoglobin dropped to 40-50 per cent. Rehospitalization on 11-1-42 because of gastro-intestinal bleeding for 8 days and precordial pain for four days. Hemoglobin 42 per cent, blood pressure 90/60, cardiac rate 120 min. On 11-2-42 she suddenly developed clinical picture of shock and pulmonary edema and died. Repeated electrocardiograms showed changes of acute coronary insufficiency manifested by RS-T depressions and T wave inversions.

Postmortem examination (P.M. #12315) showed very extensive subendocardial myomalacia, marked aortic stenosis, and coronary arteriosclerosis with moderate narrowing. There was no recent or old occlusion of the coronary arteries.

The photomicrograph shows an intact endocardium (A) and focal myocardial infarction in the subendocardial region (C) as evidenced by homogenization, loss of striation and necrosis of the myocardial fibers and reactive cellular infiltration. Between the endocardium and the necrotic area there is a zone of normal appearing myocardium (B).

In the presence of aortic stenosis with long standing diminished coronary flow, the acute hemorrhage and shock produced severe myocardial ischemia and extensive myomalacia despite the normal coronary arteries.

Proper management of shock and anemia following acute hemorrhage is essential for the prevention and treatment of coronary insufficiency. When the coronary circulation is already impaired, even a moderate drop in blood pressure or in hemoglobin concentration may be sufficient to produce myocardial anoxemia and even infarction. Active treatment with repeated blood transfusions is indicated. Clinical recovery usually is complete if the source of hemorrhage is controlled.

*Acute coronary insufficiency due to embolism of the pulmonary artery.* The report of McGinn and White, in 1935 (22), instigated intensive study of the cardio-

vascular sequelae of pulmonary artery embolism. Until recently (23), right ventricular strain (acute cor pulmonale) incident to embolic obstruction of the pulmonary artery has been so greatly emphasized that the fact that the left ventricular musculature may be more affected than the right has been almost overlooked. During the past few years, a number of reports (24-27) have appeared which emphasize the myocardial effects of embolization and point out that these effects are the result of either protracted or recurrent episodes of coronary insufficiency. In our experience this involvement has been encountered frequently and we have found that the electrocardiographic pattern of coronary insufficiency is to be seen more often than that associated with acute cor pulmonale.

Several factors contribute to the development of acute coronary insufficiency and acute myocardial alterations in pulmonary embolism. In pulmonary embolism there is a rise in pressure in the pulmonary artery and a reflex drop in systemic arterial blood pressure. Obstruction of the pulmonary artery with associated shock and drop of aortic blood pressure, reflex pulmonary arteriolar constriction, possibly vasovagal reflexes, all lead to diminution of coronary blood flow.

The patient may succumb immediately. If he does not and is subjected to recurrent episodes of pulmonary artery embolization, anoxia and myocardial ischemia are inevitable and myocardial necrosis may appear, particularly in individuals who have a structural abnormality of the heart such as coronary arteriosclerosis or myocardial hypertrophy. Cardiac sequelae of embolism of the pulmonary artery are seen most often in hearts which are the site of widespread arteriosclerosis with associated narrowing of the lumen of the affected coronary arteries. Less frequently the hearts of patients with cardiac hypertrophy who had suffered recurrent embolism showed myocardial damage without significant arterial narrowing.

In human hearts these pathological changes most often involved the wall of the left ventricle, occasionally the left and right ventricles simultaneously, rarely the right ventricle alone. This finding indicates that the left ventricular musculature is more susceptible than the right to the effects of acute coronary insufficiency.

Although right ventricular strain and dilatation undoubtedly occur it is apparent that dilatation of the right side of the heart is not invariably a sequel to acute pulmonary artery occlusion.

The electrocardiographic pattern that has been ascribed to pulmonary embolism arising from acute right ventricular strain and dilatation, is characterized by deep S-1 and Q-3, RST depression in lead I and elevation in lead III, transient intraventricular block, inversion of T-3, or of T-2 and T-3, and delayed inversion of T-4 (22, 28). We have found, however, as have other observers (29, 30), that these classical alterations occur in a minority of cases and that the pattern typical of acute coronary insufficiency, i.e., RS-T segment depressions and T-waves inversions appears more commonly (5, 7, 31).

In an analysis which we have made of 40 fatal cases of pulmonary embolism

confirmed by autopsy, electrocardiographic signs characteristic of acute cor pulmonale appeared in only 14 cases (fig. 4). In 17 cases depression of RS-T segments and inversions of T-waves were noted, in the absence of S and Q waves and RS-T elevations (fig. 5). Of the remaining 9 cases, 6 showed atypical QRS and T changes, and 3 no alterations whatsoever. Electrocardiographic evidence of acute coronary insufficiency was more frequent and striking in the older age

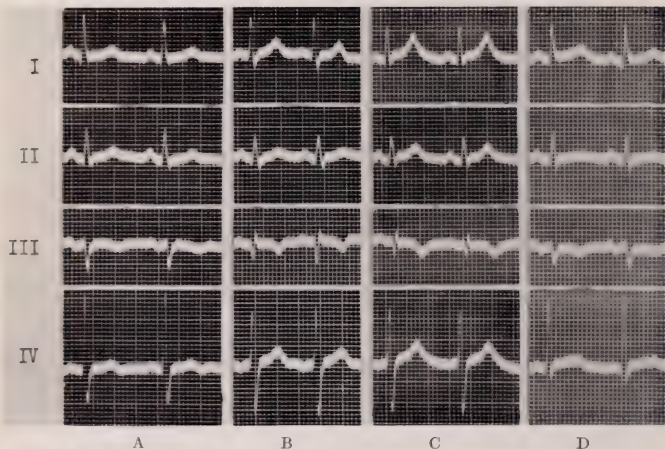


FIG. 4. F. P. (Adm. #407391) Acute cor pulmonale due to acute pulmonary embolism in a male aged 69. Six days after cystoscopy two episodes of pulmonary infarction occurred on April 27, 1937 and on May 3, 1937, manifested by chest pain, dyspnea, cyanosis, cough, fever, drop in blood pressure, bilateral pulmonary consolidation and friction rub. On May 19, the patient suddenly went into severe shock and died. Autopsy revealed organizing emboli in both pulmonary artery branches and a recent embolus in the right branch, with organizing pulmonary infarcts. The coronary arteries were moderately sclerotic and narrowed. There was evidence of chronic rheumatic mitral and aortic valvular disease.

The ECG of 4 27 37 (A) is normal. The clinical pattern of acute cor pulmonale developed on 5 3 (B) and 5 4 37 (C), consisting of small S1 and deep Q3, deeply inverted T3 and "staircase" RS-T segments in leads I and II. The changes are transient and disappear by 5 10 37 (D).

group and in those patients with antecedent heart disease than in the other groups.

Post-mortem examination revealed focal subendocardial or papillary muscle necrosis or ischemic changes in approximately one fourth of the 40 cases. Morphologically, the lesions differed in no respect from those usually seen following coronary insufficiency induced by shock and hemorrhage (4, 5, 11). The involvement was, in most instances, confined to the wall of the left ventricle especially the posterior wall. Occasionally the right ventricular muscle was the site of focal ischemic changes. The incidence of myocardial necrosis was as frequent



in the group presenting the electrocardiographic pattern of acute cor pulmonale as in the group presenting the picture of coronary insufficiency.

On the basis of electrocardiographic and anatomical observations, we believe that the mechanism of acute coronary insufficiency may be the dominant factor determining the cardiac effects of acute pulmonary embolism. The contrasting electrocardiographic patterns of acute cor pulmonale and acute coronary insufficiency following pulmonary embolism are illustrated in figures 4 and 5.

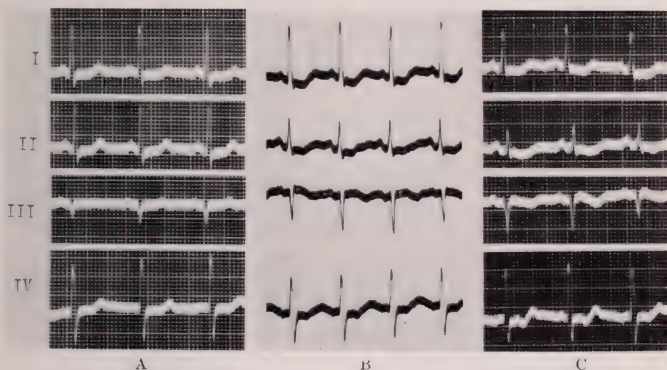


FIG. 5. L. H. (Adm. # 494959) Acute coronary insufficiency due to pulmonary embolism in a woman aged 53 years. On Sept. 19, 1942, five days after gastrectomy for carcinoma she developed shock, dyspnea, cyanosis, tachypnea and tachycardia. She died in congestive heart failure six days later (9/25/42). Autopsy disclosed embolism of the right pulmonary artery and healed mitral and aortic rheumatic valvulitis. The coronary arteries were widely patent and only slightly sclerotic. The myocardium presented no acute changes. A. The preoperative ECG 9/10/42, is normal except for slight RS-T depression in leads I and II.

B. 9/19/42 Sinus tachycardia, striking depression of RS-T and diphastic T-waves in leads I, II and IV. These changes are characteristic of acute coronary insufficiency.

C. 9/23/42 The RS-T depression is less marked.

#### PREVENTION AND TREATMENT

Appreciation of the significance of acute coronary insufficiency as a clinico-pathological entity is necessary for prevention and for adequate treatment of this condition. A question may arise of the clinical value of differentiating myocardial infarction due to coronary occlusion from myocardial infarction due to acute coronary insufficiency, since the systemic effects of both types of infarction differ only in degree. In answer, it may be pointed out that clinically, physiologically, anatomically and therapeutically it is unsound to apply one term to the two conditions. The therapeutic approach to each differs in several important respects and the etiological mechanisms involved are entirely dissimilar.

In acute coronary insufficiency active and vigorous measures in the early stages, directed toward removal or amelioration of the precipitating factor, may

be successful in diminishing the myocardial ischemia or anoxia, and thereby preventing myocardial infarction. When infarction has occurred elimination of the coronary insufficiency by appropriate therapy will prevent further cardiac damage. In acute coronary occlusion on the other hand, therapy is necessarily symptomatic; it is not based on specific measures or directed toward a special precipitating factor. It is worthy of emphasis that measures ordinarily contraindicated in acute coronary occlusion may be of benefit in acute coronary insufficiency.

Treatment in acute coronary insufficiency depends almost entirely on the nature of the precipitating factor. As soon as this factor can be ascertained in any given case, active treatment should be instituted toward elimination of the factor and improvement of the coronary circulation. For example, when increased cardiac work is the cause of acute coronary insufficiency it is important to remove any undue physical or emotional strain from which the patient may be suffering. Paroxysmal tachycardia may be terminated by vagopressor drugs, quinidine, or digitalis. In a hypertensive crisis, measures to decrease blood pressure, such as vasodilators and phlebotomy are urgently indicated. In thyrotoxicosis, adequate medical treatment, and often thyroidectomy, are required to restore normal coronary circulation.

In acute coronary insufficiency due to diminished coronary blood flow the treatment revolves about the proper management of shock and hemorrhage. Restoration of circulatory blood volume, arterial blood pressure and hemoglobin level by measures such as intravenous administration of blood is requisite. Although these measures may appear heroic and even harmful in a clinical condition which simulates acute coronary occlusion, nevertheless active treatment of shock and hemorrhage should be undertaken, particularly in patients of the older age groups whose coronary artery circulation is chronically deficient.

Efforts to prevent postoperative coronary insufficiency and myocardial infarction should be directed toward maintenance of normal blood volume and blood pressure, the control of dehydration and of local or systemic infection. Slow intravenous administration of saline solution or blood pre- and postoperatively may be of prophylactic value for any patient in whom coronary insufficiency seems a possible complication. During operation, anoxemia due to excessive anesthesia should be avoided.

#### SUMMARY

The concept of acute coronary insufficiency as a clinical entity is presented. The physiological mechanisms involved are discussed. The etiological background, pathological criteria, clinical picture, electrocardiographic patterns, and therapy are described.

Acute coronary insufficiency may be produced by any factor which induces sudden transient or protracted disproportion between the nutritional requirements of the myocardium and the coronary blood flow. Predisposing factors may be structural, such as coronary arteriosclerosis, arteriosclerotic and luetic aortic stenosis, aortic valvular disease, cardiac hypertrophy; or they may be

functional such as chronic anemia, hypothyroidism, chronic congestive heart failure. The precipitating factors are: (a) increased cardiac work due to severe exertion, emotional stress, tachycardia, hypertensive or thyroid crisis, acute infectious states or adrenalin. (b) Diminished coronary artery blood flow due to shock, hemorrhage, sudden drop in blood pressure. (c) Anoxemia due to anesthesia, carbon monoxide poisoning, pulmonary embolism, acute anemia, and bronchial asthma. (d) Any combination of these factors.

The pathological picture is one of subendocardial focal necrosis involving primarily the posterior wall, septum and papillary muscles of the left ventricle. This may vary from microscopic lesions to a more extensive predominantly subendocardial infarction. Although varying degrees of coronary arteriosclerosis and narrowing of the lumen may be present, acute coronary occlusion is never found.

The electrocardiogram in acute coronary insufficiency is characterized by temporary S-T segment depressions and T-wave changes in one or more leads, with usual reversion to normal after elimination of the precipitating factor. Unlike the electrocardiogram in acute coronary occlusion, S-T elevations and deep Q-waves are very rarely encountered.

The clinical picture may be asymptomatic or vary from one of simple angina pectoris to conditions resembling myocardial infarction due to acute coronary occlusion. On the other hand, precordial pain may be absent, and the diagnosis detected solely by the electrocardiogram, knowledge of the precipitating factor, and response to therapy.

In general, active and vigorous measures in the early stages of acute coronary insufficiency, directed toward removal or amelioration of the precipitating factor, may be successful in diminishing the myocardial ischemia or anoxia, and thereby preventing myocardial infarction. When infarction has occurred elimination of the coronary insufficiency by appropriate therapy will prevent further cardiac damage.

Shock, particularly in the older age group, is a common cause of acute coronary insufficiency because it produces a diminution of coronary blood flow. When the myocardial ischemia is severe and prolonged subendocardial infarction may result. Shock following surgical procedures, trauma, hemorrhage, spinal anesthesia, pulmonary embolism, ruptured abdominal viscus, acute infections, hypertensive and hypotensive crises, have resulted in acute coronary insufficiency.

Slow intravenous administration of saline solution or blood pre- and post-operatively, may be of prophylactic value for any patient in whom coronary insufficiency seems a possible complication. During operation anoxemia due to excessive anaesthesia should be avoided.

*Acute hemorrhage* is almost as frequent a precipitating cause of acute coronary insufficiency as is medical and surgical shock. Since this variety of acute coronary insufficiency is so amenable to treatment, recognition of hemorrhage as a precipitating cause is of paramount importance.

Although the acute coronary insufficiency is generally more striking if the acute

anemia is profound, the decreased blood volume resulting from the hemorrhage is regarded as the major mechanism. The factors responsible for precipitating the acute coronary insufficiency in hemorrhage were the degree of shock, drop in blood pressure, tachycardia, and decrease in hemoglobin level. It is our impression that the proper management of shock and anemia following acute hemorrhage is essential for the prevention and treatment of coronary insufficiency. Active treatment with repeated blood transfusions is indicated. Clinical recovery usually is complete if the source of hemorrhage is controlled.

In pulmonary embolism, the left ventricle is frequently involved as a result of acute coronary insufficiency. Shock, drop in systemic blood pressure, anoxemia, possibly coronary artery reflex mechanisms, result in anoxia of the myocardium and diminution of coronary flow.

The electrocardiographic pattern of acute right ventricular strain and dilatation, i.e., deep S-1 and Q-3, was not so commonly encountered in pulmonary embolism as was that of acute coronary insufficiency, i.e., RS-T segment depressions and T-wave inversions. Morphological evidence of coronary insufficiency in the form of focal infarction of the left ventricle was found in approximately one-fourth of the cases.

The mechanism of acute coronary insufficiency may be the dominant factor determining the cardiac effects of acute pulmonary embolism.

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## RADIATION THERAPY IN EARLY LARYNGEAL CANCER<sup>1</sup>

RUDOLPH KRAMER, M.D.

This is a report of my observations on the treatment of limited cancerous growths of the larynx by the protracted fractionated x-ray technic. For the evaluation of the results noted, a survey of certain phases of the subject of laryngeal cancer is necessary. In this way, we shall be able to compare the results of surgical therapy with those indicated by my observations of radiotherapy.

The term "limited," as used in this report, requires definition. It is applied to a small cancerous lesion with no detectable lymph node metastases. It is presumably an early lesion as a rule, but it is possible that, because of the peculiarities of early laryngeal growths, it may present the characteristics of a limited lesion and nevertheless may have been present for many months. It is important to emphasize that the term "limited" as used here, applies only to spatial dimensions. It is applicable to lesions anywhere in the larynx. Under certain circumstances it is necessary to add to the term "limited," the designation of the location of the growth in the larynx. This is best exemplified by the requirements of laryngeal surgery. There are two basic procedures in the surgery of laryngeal cancer, laryngofissure and laryngectomy. The indications for laryngofissure are a limited lesion of the true vocal cords with sufficient normal tissue posteriorly to permit resection of the cord beyond the cancer. It has been found that in addition to the above, laryngofissure is applicable if the growth involves the anterior commissure and even a small anterior portion of the opposite cord. Thus we have here a limited lesion of a definite portion of the larynx, the more anterior portion of the true vocal cord. A limited lesion of parts of the larynx other than the one mentioned above, is generally treated by laryngectomy, that is, total extirpation of the larynx. It is evident therefore, that determination of the exact site of limited lesions is of paramount importance in the selection of the appropriate surgical procedure.

In laryngofissure the thyroid cartilage is slit, the growth removed and the larynx closed. By this method most of the laryngeal structures are retained, affording adequate airway for respiration and a more or less useful voice. Laryngectomy entails the removal of the larynx, permanent tracheotomy and the loss of laryngeal voice. The distinction between true cordal and extra-cordal "limited" lesions is the tendency to more rapid involvement of the lymph nodes in the latter group in contradistinction to the late involvement of the nodes in anterior true cord growths. For this reason, laryngofissure is generally applicable to anterior or true cord lesions but it is recognized that this procedure is not applicable to a growth of the same size involving, for example, the false cords or posterior portion of the true vocal cord. The usual practice therefore is to perform a laryngectomy in these extra-cordal lesions.

<sup>1</sup> Lecture given at the Graduate Fortnight of the New York Academy of Medicine on October 17, 1946 at the Blumenthal Auditorium of The Mount Sinai Hospital.



The very early onset of hoarseness in true cord lesions leads to their recognition while they are in their incipiency, if the physician is alert and thorough in his examination. Because of the early recognition brought about by hoarseness and the tendency to lymph node metastasis only late in the course of the disease, the results of laryngofissure in these cases are excellent. Many series of these cases have been operated upon with 70 per cent to 85 per cent cures or rather, freedom from disease.

The extra-cordal "limited" cases do not reveal themselves early by hoarseness because the true vocal cords are not involved. These lesions are manifested usually by a slight soreness or irritation of the throat, rasping, clearing of the throat or discomfort on swallowing. If examined at this point in the patient's history, a limited extra-cordal growth may be discovered; otherwise, it will progress until large portions of the larynx are involved with extension to the vocal cords when hoarseness ensues, or the extrinsic larynx may be invaded with resultant pain and dysphagia or finally, lymph node metastases are evident. The last is a common finding in these cases. Of course the "limited" growths of the posterior portion of the true cords cause hoarseness as early as the anterior cordal growths. These cases as I have stated before, are treated by removal of the larynx *in toto*. I know of no reports on laryngectomized patients in which the results in "limited" lesions are separated from those with extensive lesions.

In 1931 Dr. William Harris, radiotherapist to Mount Sinai Hospital, brought to my attention Coutard's work on fractionated protracted Roentgen therapy for cancer of the larynx. The first case was successfully treated in 1931 at this hospital. The patient had an inoperable cancer of the extrinsic larynx. The cancer was eradicated by radiotherapy and the patient is still alive and well 15 years later. At first, this method of treatment was used only on inoperable cases. This was to be expected as relatively little was known of its action and application. Other patients were then treated, practically all of them inoperable or advanced cases. One patient with a "limited" growth was treated in these early days by radiation rather than surgery because of severe coronary disease. He became free of disease and survived for 10 years with no recurrence. However, it was difficult to take the next step and refer fissure cases for the new treatment with radiotherapy. The surgical procedure, laryngofissure, was relatively safe, quick and sure, radiotherapy was prolonged in time and in discomfort and the results were not definitely established. The first case, in 1932, of a cordal type treated by radiotherapy was a private patient and the result was a most unfortunate failure. The growth was of the type that could be treated by laryngofissure but it was decided to treat him by protracted radiation instead. Six months later it was evident that no cure was obtained by this method and surgery was advised. The patient and his physician were justifiably through with me and my advice. They went elsewhere. There were numerous repercussions for this failure because the leading laryngologists in great part were dead set against this treatment and here was a spectacular failure to add to the support of their views. However I persisted in recommending radio-

therapy to all patients with cancer of the larynx. None were excluded from treatment because of severity or extent of disease or for any other reason except some fissure cases. In 1938 I reported at the Laryngological section of the Academy of Medicine, the results of fractionated radiotherapy of ward and private patients treated for me by Dr. William Harris. The material discussed included all the patients seen who assented to therapy and was composed mainly of cases of extensive and inoperable disease with a few cases of limited lesions. The results in this group of cases where only limited cases were excluded, were shown to be far superior to those obtained by surgery in unselected and consecutive cases. These results were as good as the best laryngectomy series reported in which the cases were strictly selected according to operability.

As a result of these studies, I decided to advise all patients with limited growths to have radiotherapy despite the failure to cure the first case in the early days of the procedure. There are three objections to the use of radiotherapy in limited cancer of the larynx aside from the question of results.

- 1) The first is the longer period of time required to complete the therapy as a rule.

- 2) The second objection is the longer period of discomfort and pain during and following radiotherapy as compared with laryngofissure.

- 3) The third objection is the appearance of edema of the larynx, particularly of the arytenoids in some cases, during the first year after radiotherapy, rarely during the second year. This is manifested by irritation of the throat, soreness, some dysphagia and hoarseness. It is most often due to vocal strain, rarely to excessively hot foods. The edematous condition may last for weeks before disappearing.

Against these objections are to be weighed the following factors in favor of radiotherapy.

- 1) Fractionated radiotherapy is used as an office procedure obviating hospitalization. The social and economic advantages which accompany ambulatory treatment may be important in many instances.

- 2) The retention of the larynx in toto and the negligible effects on the voice as a result of radiation therapy are preferable to the effects of laryngofissure.

- 3) There are dangers inherent in a surgical procedure involving the respiratory tract even though the procedure is as innocuous as laryngofissure performed under local anesthesia. This is particularly the case when dealing with patients of advanced age and patients with severe systemic disease. These dangers are not encountered in properly administered radiotherapy.

- 4) The psychic effects of the type of therapy used are often tremendous. Most, if not all patients, are affected adversely either by the thought of or by the early period of laryngeal surgery. In some instances a state of panic ensues in which death is preferred to surgery. No attempts at persuasion or reassurance I have used have been successful in calming a few of these patients. The psychic effects noted when surgery was advocated or used, are not seen when radiotherapy is the method of treatment. To the layman, surgery

brings to mind all the horrible implications of cancer. For some strange reason, this is not the situation when radiation is employed.

However these pros and cons are only valid if the results of fractionated radiotherapy are comparable with those of surgery. Let us therefore examine the results of treatment. Dr. Harris has treated 32 cases of limited laryngeal cancer that I have followed.

21 were private patients and 11 were ward patients.

13 patients are free of disease from 5 to 11 years.

9 more are free of disease from 3 to 5 years.

6 more are free of disease from 1 to 2 years.

28 of 32 are free of disease from 1 to 11 years.

Of 22 suitable for fissure, 2 were failures.

Of 10 which would have required laryngectomy, 2 were failures.

Of the 4 radiotherapy failures in the series, one died of a coronary attack after 20 months of freedom from cancer, one, noted in the early part of this report, was a radiation failure but was cured by laryngectomy. The 2 remaining patients died of cancer, that is they were also failures. These three failures and an additional statistical failure, the patient who died of a coronary attack, represent 12½ per cent of the series. In other words, the results of fractionated radiotherapy in limited laryngeal cancer are as good as the best of laryngofissure series.

There will be immediate objection to the inclusion of the 6 cases of 1 year freedom from disease as valid cases of cure. Since 1931 we have seen no case of reappearance of disease after 1 year of freedom from disease. In fact, seven months is the longest interval between treatment and definite evidence of failure to eradicate the lesion. There is no doubt in my mind that there will be cases in which recurrence will take place 1 to 20 years after apparent cure. But up to the present, the 1 year result can be used as an indication of the general status of radiotherapy but not of surgery of cancer of the larynx. This view is based on the tendency of surgically treated cases to manifest a recurrence one or more years after apparent freedom from disease. In other words, radiotherapy failures are apparent at once or shortly after treatment has been completed, whereas surgical failures may become apparent after years of freedom from disease.

If we consider the number of patients free of disease for 3 or more years, we find that 22 of 26 patients treated 3 or more years ago are free of disease. The 4 failures listed occurred in patients treated over 3 years ago. The results, 22 free of disease in 26 patients treated, approximately 85 per cent, are as good as the best results of laryngofissure. The application of statistics and percentages in such a small group is not valid but it is employed simply to indicate a trend towards certain results and not as a method of accurately delimiting certain features.

In conclusion, I must make it clear that these results are based on the application of fractionated protracted radiotherapy by one man, Dr. William Harris. They depend on the dosage and application used by him. Whether these are the same or different factors used by others, I do not know. The work of other

radiotherapists is not included in this report. It can be suspected that the dissatisfaction of some laryngologists with radiotherapy may in part be ascribed to the radiation technic employed. An additional factor may be the patient who was unsuccessfully treated by radiation and who then makes the rounds of a number of laryngologists. In this way the impression is gained of a number of failures by skilled radiotherapists. I am quite sanguine about the future of this method of treatment of laryngeal cancer until the day when a specific cure of cancer is found.

# INFUNDIBULOMA\*

## A CASE REPORT WITH A REVIEW OF THE LITERATURE

BERNARD D. FINE, M.D., AND ALVIN I. GOLDFARB, M.D.

[New York, N. Y.]

A previously unrecognized type of tumor of neurohypophyseal derivation was first reported by Globus (1) in 1942. The tumor was therefore named infundibuloma because it simulated the structure of the infundibulum and the neurohypophysis, and possessed a vascular pattern similar to that of the infundibular region in which it originated. Two such cases were recorded by Globus, and since then another was described by Papez and Ecker (2).

It is reasonable to assume that tumors of this type were in existence before, and have been overlooked and placed into other categories. Thus, it is highly probable that occasional tumors found in the neurohypophyseal region and described as vascular gliomas, central neurinomas, and gangliomas may well belong to the group of infundibulomas. For this reason, a report is warranted of another case in which a tumor in the hypothalamic-suprasellar-region presents the gross and microscopic features of infundibuloma.

### CASE REPORT

*History.* (Adm. #535055; P.M. #13158; Surg. #88470) The patient, a 6 year old boy, developed normally and aside from uncomplicated intercurrent measles, mumps and chickenpox was apparently well until the onset of his terminal illness. His maternal grandmother died of a brain tumor, and his paternal great-grandmother was operated on for the removal of a brain tumor. One year before admission to the hospital, he developed a left external strabismus and progressive diminution of vision in his left eye. Ten months later he began to have frequent episodes of vomiting. In another month he began to complain of headaches chiefly localized to the left side of the head. At this time weakness of his right upper extremity appeared. Two days before admission, his parents noted increasing mental confusion, marked ataxia and inability to retain solid or liquid food. He entered the Mount Sinai Hospital on May 29, 1945.

*Examination.* The child was drowsy with brief periods of alertness. The left eye was deviated nasally. The pupillary reactions were inconstant, varying from fixation in wide dilatation bilaterally to a normal reaction to light on the right, with only a consensual response on the left. There was papilledema of 1D in the right eye, and a more chronic papilledema with secondary atrophy, exudates and a small area of hemorrhage in the left eye. A right temporal hemianopsia with complete blindness of the left eye was found although cooperation was poor. The patient's head was fairly large and on percussion yielded a positive McEwen sign. He displayed a generalized hypotonia, slightly more marked on the right side. He had a slight right hemiparesis and on finger-to-nose test he showed moderate ataxia bilaterally. There were suggestive Babinski signs bilaterally.

*Laboratory data.* X-ray examination of the skull showed marked diastasis of sutures with considerable erosion of the dorsum sellae and posterior clinoids. There were no intracranial calcifications. Changes were noted which were interpreted as those of a marked increase of intracranial pressure.

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\* From the Neuropathological Laboratory of The Mount Sinai Hospital, New York.



Electroencephalography showed a very large amount of delta activity with frequencies as low as 1 per second, and a voltage as high as 250 microvolts appearing all over the brain, more at the indifferent and occipital than at the other electrodes, and more at the left than at the right occipital electrode. The record was considered to be highly abnormal, and was thought to favor a posterior fossa tumor over a diencephalic lesion.

*Course.* The diagnostic possibilities considered were suprasellar tumor (craniopharyngeoma), neoplasm of the brain stem, and multiple hemangiomas. Ventriculographic study showed an enlargement of the chiasmatic sulcus with dilated lateral ventricles which were encroached upon from below and rostrally, more so on the left. The third ventricle was not filled. Free communication between the lateral ventricles was established by the passage of dye. The ventriculograms were interpreted as being diagnostic of a glioma of the optic chiasm.

*Operation.* On June 8, 1945, an exploratory craniotomy was performed. On retracting the frontal lobe, the right optic nerve was seen to be crossed by abnormal arteries. Beneath it was a fleshy tumor which extended to the sella turcica and beyond toward the left side. Part of the tumor was excised, during which procedure the third ventricle was entered. Following the operation the patient's temperature rose to 104.8°F. and his pulse to 200 per minute. There was no response to the usual anti-pyretic measures. A lumbar puncture was done the next day and the pulse dropped to 88, the temperature to 99.4°F. The following morning the temperature and pulse rose again and the patient expired suddenly.

*Necropsy findings.* *Gross.* The brain weighed 1550 Gms.; it was soft and the gyri were flattened. In the interpeduncular space there was a yellowish-pink, soft, fleshy tumor, extending caudad to the midbrain and almost completely replacing the hypothalamus. The right optic nerve seemed to be enveloped by the tumor. The left optic nerve could not be recognized except at the optic foramen. The optic chiasm was not visible. The right cerebral peduncle was stretched, the left partly enveloped by the tumor.

On sectioning of the brain, a large yellow tumor mass presenting a very moist surface was found fused with the floor of the third ventricle (fig. 1). Just below the zone of fusion the tumor exhibited a large area of necrosis. The floor of the ventricle was raised so that it almost completely obliterated the third ventricle. The mass was irregularly spherical in outline and measured 4.5 cm. in its long diameter. The pituitary gland was somewhat flattened, but was otherwise not abnormal.

*Microscopic observations.* Sections of the tumor mass revealed a highly cellular, moderately vascular tissue resembling in structure and cellular pattern the posterior lobe of the hypophysis and the infundibular stalk. In many areas, there were aggregations of thin walled vessels, many of which were curved and branched in a "cork-screw" manner with the characteristic "gliogenous" investment reminiscent of embryonal and post-natal infundibulum and hypothalamic floor (fig. 2a). These vessels were present particularly in the portion of the tumor just below a normal ependymal lining of the floor of the third ventricle. In this region there was also marked engorgement of vessels with considerable extravasation of blood into the surrounding tissue. Not far from these dilated vessels there was an extensive area of necrosis in which the tissue structure was destroyed and replaced by degenerating red blood cells.

Sections of main body of the tumor, stained by the Nissl method, consisted of fusiform cells with long and tapering processes (fig. 2b). These cells were arranged in groups, especially in the vicinity of vessels, so as to surround vascular channels, or to form long, broad strands. In several areas these cells formed channels and cords, some of which had central openings. The sinusoids were lined by similar fusiform cells.

Special stains, including the Globus modification of Hortega variants I, II, III and Cajal methods, did not reveal the presence of any glial elements but again demonstrated the elongated fusiform nature of these cells. Elastic van Gieson stains brought out strikingly the characteristic form of the blood channels (figs. 3a, 3b and 4a).

There was no significant histological abnormality of the pituitary gland in either the anterior or posterior lobes.



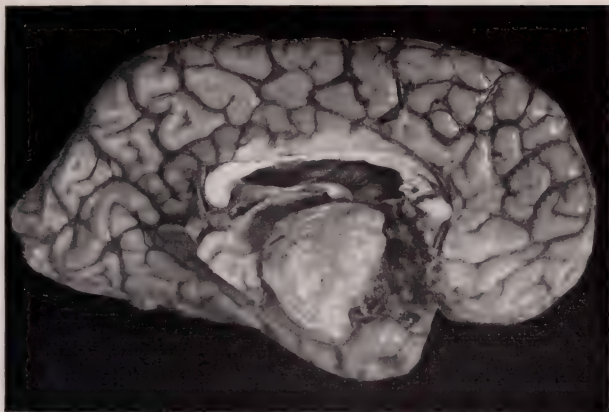


FIG. 1. Sagittal section showing medial aspect of the left hemisphere. The large fleshy tumor is seen displacing the third ventricle upward and distorting the fornix. The lateral ventricle is dilated and the anterior portion of the third ventricle is obliterated.

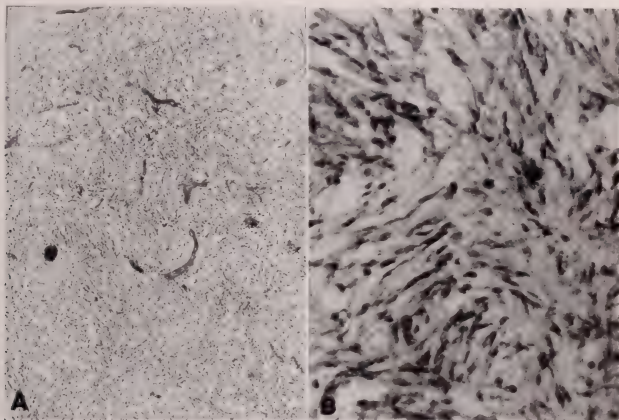


FIG. 2a. The histologic structure and vascular pattern of the tumor. Elastica van Gieson stain (photomicrograph,  $\times 40$ ).

FIG. 2b. The histologic structure of the tumor. Nissl method (photomicrograph,  $\times 300$ ).

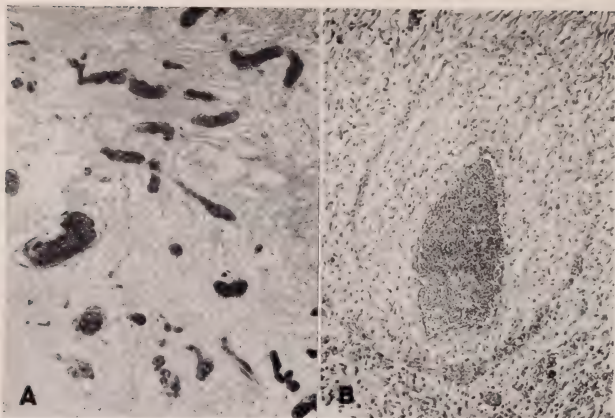


FIG. 3a. The vascular pattern and typical vessels of the tumor. Elastica van Gieson stain (photomicrograph,  $\times 80$ ).

FIG. 3b. A typical vessel of the tumor showing cellular orientation and perivascular coat. Elastica van Gieson stain (photomicrograph,  $\times 200$ ).

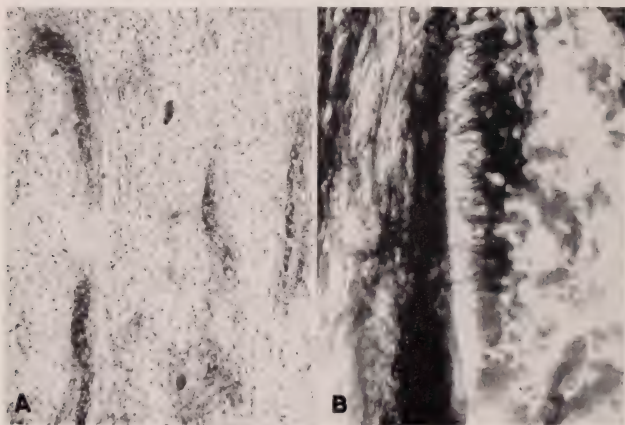


FIG. 4a. The typical vessels of the tumor, particularly demonstrating the perivascular glial coat. Elastica van Gieson stain (photomicrograph,  $\times 150$ ).

FIG. 4b. Vessel of tumor with surrounding cells showing processes extending to vessel wall ("vascular feet"). Globus modification of Hortege stain (photomicrograph,  $\times 250$ ).

*Comment.* The dominant features of the tumor were: the fairly dark-staining, elongated nucleus with a tapering cell body of homogeneous pinkish cytoplasm with markedly elongated processes, and the arrangement and structure of blood vessels in the tumor. The latter were characterized by the "cork-screw" vessels mentioned above and small sinusoidal blood vessels with thin, poorly differentiated walls, as well as small groups of vascular channels set off from the surrounding tissue by a fine, fibrillar zone. There were variations from the predominant cell type mentioned above with a moderate number of oval or rounded vesicular nuclei which in several areas were arranged in small sheets. The numerous sinusoidal channels (resembling "vascular lakes" as described by Globus) were usually in areas showing large and small hemorrhages, tissue disorganization and many macrophages containing brownish pigment.

#### DISCUSSION

The literature since 1930 was reviewed with the aim of finding any recorded tumor in and around the third ventricle which might possibly be considered as falling into the category of infundibuloma on the basis of the gross and microscopic description or illustrations. Case reports indexed under the titles of tumors of the hypothalamus, tumors of the floor of the third ventricle, gliomas of the optic chiasm, central neurinomas, gangliomas of the third ventricle, and polar spongioblastomas at the base of the brain were selected for scrutiny. In general, this survey gave unsatisfactory information because of the brevity of the microscopic descriptions and the inadequacy of illustrations. However, the cases originally collected from the literature by Globus (1), especially the case of Hamby (3) (in which the microscopic description was definitely suggestive of infundibuloma), as well as Case 65 in the series of Bailey, Buchanan and Bucy (4), and Case 17 of Bailey and Eisenhardt (5), still remain probable additional examples of infundibuloma. Our own survey disclosed several case reports which may be regarded as suggestive of infundibuloma. Among these are: 1. a Cabot Case (6) presented at the Clinical Pathological Conference of the Massachusetts General Hospital diagnosed as hypothalamic tumor in an 11 year old girl; and 2. a case report of Lhermitte and his associates (7) of a similar tumor in a 9 year old girl, but the microscopic evidence in both cases was not sufficient to justify any positive statement without a review of the sections.

The most striking feature of these tumors, as seen in this case and in Globus' two previous cases, is the unique vascular pattern. We feel that microscopic study of tumors occurring in the hypothalamic region with special reference to their blood vessels and cellular structure will reveal additional cases that can be properly classified as infundibuloma.

Globus had noted originally that the tortuous "corkscrew" vessels with their characteristic glial sleeves, seen only in the infundibulum, are the most characteristic feature of infundibulomas. In 1932, he and his co-workers (8), at that time unaware that similar observations had previously been made by Popa and Fielding (9), described peculiarly constructed blood vessels in the tuber cinereum and infundibular stalk. These observations, together with later studies, estab-

lished their vascular pattern as a definite anatomical landmark of the infundibular region.

In the original work by Globus (1), a special study was undertaken to determine the developmental changes in these vessels during the early post-natal months. The same typical vessels were found in the brains of infants from birth until the sixth month of post-natal life. Following this period, an involution of their structure occurs so that the distinct pattern is less clearly discerned.<sup>1</sup> These vessels, because of their peculiarity and regional limitations, invited investigations as to their probable function. Thus Popa and Fielding suggested that they form part of a "hypophyseal-portal circulation." With some reservations (primarily in reference to their anatomical relations and the direction of blood flow in these vessels), this view was accepted by Wislocki and his co-workers (10, 11). In investigations carried out both on monkeys and man, they demonstrated that the venules comprising this portal system arise from a capillary bed located around the periphery of the infundibular stalk and connect the latter with the sinusoids of the anterior lobe of the hypophysis. They also demonstrated that the vascular net of the stalk was separated anatomically and physiologically from the general brain blood vessel net of the hypothalamus except by a few small capillaries. It seems, therefore, that this vascular network should be considered separate from that of the brain, and that the infundibulum can be recognized readily by its unusual blood vessel pattern.

The three proven cases of infundibuloma from this laboratory do not allow more than a few suggestions as to the characteristic clinical features of these tumors. The cases, however, do present certain clinical similarities which are deserving of attention in considering the differential diagnosis of tumors in and around the third ventricle (table 1). These are: 1) age—all cases have been in the pre-pubescent age group (5, 6 and 13½ years); 2) local pressure signs, i.e., pupillary changes, external ocular muscle palsies, hemianopsia; 3) signs and symptoms of increased intracranial pressure, i.e., headache, vomiting, papilledema, drowsiness; 4) x-ray examination of the skull showing erosion of the sella turcica<sup>2</sup> and 5) the lack of striking evidence of endocrine or vegetative signs or symptoms such as might be expected in a tumor in this region. These criteria obviously fall far short of allowing definitive clinical diagnosis of these tumors, especially in view of the small number of cases described to date. However, it is hoped that they will at least serve as a rough guide to their further study and differentiation.

In reference to the relative absence of vegetative or endocrine disturbances, there are several features of interest in these cases. A microscopic characteristic of the tumor in this case, as in the two cases previously reported by Globus (1),

<sup>1</sup> In connection with these observations, Globus noted in one instance in the brain of a 49 year old man, diagnosed as a case of "Cushing's syndrome," a grouping of hypophyseal-portal vessels in a stage of development usually found in the infant.

<sup>2</sup> An additional feature which may prove to be of some diagnostic importance in these cases is the absence of local calcification in the vicinity of the sella, especially since in the series of Globus and Gang (and in the statistics of other authors) on craniopharyngeoma, well over 50 per cent of the cases show definite supra-sellar calcification.

TABLE 1  
*Outline of pertinent data in three cases of infundibuloma*  
 (Including present case)

	H. G.	E. B.	T. S.
Age	13½ years	5 years	6 years
Sex	M	F	M
Duration of clinical course	31 months	19 months	13 months
Vegetative and endocrine disturbances	Somewhat underdeveloped secondary sex characteristics	None noted	None noted
Signs and symptoms of increased intracranial pressure	Headache, vomiting, papilledema and McEwen's sign.	Headache, vomiting and drowsiness. Marked optic atrophy.	Headache, vomiting and confusion. Bilateral papilledema with secondary atrophy, left eye. McEwen's sign.
Focal signs	Right pupil larger than left, and reacts poorly to light. Right homonymous hemianopsia. Pulse and temperature dissociation.*	Right external rectus paresis; right central facial weakness. Rotary fixation nystagmus, right eye.	Left external rectus palsy. Amaurosis, left eye. Slight right hemiparesis. Right temporal hemianopsia.
Laboratory data	Blood Wasserman, negative. Lumbar puncture: initial pressure 320 mm., total protein 37 mg. per cent.	Lumbar puncture: xanthochromic fluid under increased pressure, total protein, 125 mg. per cent.	Blood Wasserman, negative. EEG showed diffuse abnormality. Lumbar puncture not performed.
X-ray	Moderate increase in size of sella with thinning of dorsum sellae. No calcification.	X-ray of skull not satisfactory. Sella approximately normal in size (?). No calcification.	Diastasis of sutures with considerable erosion of dorsum sellae and posterior clinoids. No calcification.
Ventriculography	Marked internal hydrocephalus, especially on right. Dislocation of septum pellucidum to left. Third ventricle not filled.	None done	Dilated lateral ventricles (left greater than right) and enlargement of chiasmatic sulcus. Third ventricle not filled.



TABLE 1—*Concluded*

	H. G.	F. B.	T. S.
Gross and anatomical findings	Globular mass projecting from floor of third ventricle. Tumor in interpeduncular space—in lateral wall of hypothalamic part of third ventricle.	Somewhat nodular tumor, occupying entire interpeduncular space; optic chiasm apparently buried in tumor mass. Masses projected into the foramina of Monro from the third ventricle.	A yellowish-pink, soft, fleshy tumor extending caudal to the midbrain and almost completely replacing the hypothalamus.

\* The presence of pulse and temperature dissociation as indicative of a lesion in the peri-ventricular zone of the third ventricle and in the tuber cinereum has been previously described by Globus and Strauss in an article on Tumors of the Brain with Disturbance in Temperature Regulation (*Arch. Neurol. & Psychiat.*, 25: 506, March, 1931). In this case it was probably caused as a secondary pressure effect of the large tumor in the interpeduncular space.

is its infiltrative character which probably spared vital hypothalamic tracts so that no vegetative disturbances became manifested clinically. Thus, the lack of such symptoms or signs probably can be considered to be the result of fortuitous sparing of vegetative regulatory pathways and is probably of no diagnostic importance.

The suggestion offered by Papez and Ecker (2), that symptoms of endocrine imbalance arise with such tumors only if the pituitary is uninjured, does not seem applicable in this case because in the presence of a hypothalamic tumor and a normal pituitary, there were no symptoms of endocrine dysfunction. Also, the youth of the patients thus far shown to have such tumors cannot be invoked as the explanation of the lack of signs and symptoms of endocrine imbalance in view of the report of Globus and Gang (12) on 14 cases of craniopharyngeoma. Seventy-five per cent of the eight cases under the age of 15 years had either polyuria and polydipsia, obesity of Froehlich type with hypogonadism and underdeveloped secondary sex characteristics or various combinations of these symptoms and signs. Furthermore Frazier (13) in a similar review of 14 cases of hypophyseal stalk tumors noted vegetative disturbances in a similar young age group. It is possible that pressure upon the pituitary gland contributed to the development of many of these clinical phenomena, although Papez, as previously mentioned, favors the contrary view predicating active antagonism or balance of functional activity between the pituitary and hypothalamus.

Another aspect of this tumor that requires further investigation is the final identification of the predominant cell type. Globus (1) called attention to the resemblance between the predominant cell form of this tumor and the pituicytes of the pars nervosa of the hypophysis. Bucy (14) originally described the resemblance of the cells of the pars nervosa (with their unipolar and bipolar

processes, and "vascular feet") to glia cells. He, however, remarks that in spite of their arrangement and cell form, "these cells do not resemble glia cells elsewhere in the brain." These cells are also present in the infundibulum, suggesting a probable relationship to those described in infundibuloma.

Studies which might establish the identity of the cells found in these tumors with those of the pars nervosa and infundibulum would substantially contribute to clarification of the development of these tumors, and possibly would establish the hypothesis that other tumors with similar cell forms but without the characteristic vascular pattern also fall in the group of infundibuloma.

#### CONCLUSION

A case of infundibuloma with complete clinical and pathological findings is presented. Only three other cases (two from this laboratory) have been described previously in the literature. The gross and microscopic appearance of the tumor fulfills the criteria originally presented by Globus for the diagnosis of infundibuloma.

The number of cases reported is too small to permit anything more than a few suggestions as to the possible diagnostic clinical features of these tumors: 1) age—pre-pubescent; 2) focal signs related to the optic chiasm and interpeduncular space, as well as generalized signs and symptoms of increased intracranial pressure; 3) x-ray evidence of enlargement and destruction of the sella in the absence of local calcification; 4) the apparent lack of vegetative or endocrine disturbances.

The microscopic nature of the tumor again is noted to be quite characteristic, with the unique infundibular vascular pattern and with the typical cellular structure wherein the individual cells resemble pituicytes.

The presence of the same infundibular vascular pattern in these tumors as was noted by Globus and his co-workers (2) in a previous paper on the normal infant brain, together with the association of a cellular structure resembling that of the neuro-hypophysis would point to their origin from embryonal rests in this region.

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## USEFULNESS AND LIMITATIONS OF LABORATORY STUDIES IN THE DIAGNOSIS OF VIRUS DISEASES\*

ALFRED L. FLORMAN, M.D.

The approach to an etiological diagnosis of a virus disease is, in its general aspects, similar to that traditionally employed for any infectious disease. Guided by clinical and pathological experience, an impression is gained as to the nature of the illness. An attempt is made to confirm this by recovering the causative agent from appropriate body tissues or fluids or by demonstrating the appearance during convalescence of specific antibodies. The differences which have tended to set the study of virus diseases apart are mainly those associated with the special laboratory technics (1) made necessary by the peculiar properties of viruses.

Viruses are the smallest known infectious agents and range in size, complexity and properties from the relatively simple nucleoprotein molecules of tobacco mosaic to the complex elementary bodies of vaccinia and psittacosis. These latter, when properly stained, may be seen with the oil immersion lens of an ordinary compound microscope (2). They are considered as a single group because, in addition to being very small, they multiply only in the presence of living cells. When a virus is brought to a susceptible host, the symptoms which follow reflect the affinity of that particular virus for particular cells of the host, and its tendency to bring about in them hyperplasia, necrosis, or both. Thus, by reaching, multiplying within and finally destroying the anterior horn cells of the spinal cord, one of these agents produces the familiar clinical picture of poliomyelitis. By growth within certain epithelial cells the virus of verruca vulgaris stimulates the cellular hyperplasia seen in warts, while another virus transforms epithelial cells into the pustules of small pox by combining the effects of both hyperplasia and necrosis. Viruses differ greatly in their potentialities and, in the main, it is by what they do that we distinguish one from another (3). Unfortunately, a number of them, for example those of eastern and western equine encephalomyelitis and St. Louis encephalitis, often produce clinically indistinguishable pictures. So, too, do the influenza viruses as well as those of the so-called psittacosis group. It is in such diseases that the virologist can offer most assistance to the diagnostician. However, in order for the clinician to best use the laboratory, he should understand something of the procedures which may be required to give him the desired information, as well as the type of case and specimen which may reasonably be expected to yield significant information.

*General types of virus studies which are applicable to clinical medicine.* The fact that viruses multiply only within living cells influences all laboratory work with them (4). For practical purposes this means that in order to recover a

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*virus* from a patient a susceptible small animal or chick embryo (5) must be inoculated. In addition to the usual difficulties inherent in using any biological indicator, there is the added possibility that a virus which is latent within the test animal may be provoked into activity (6, 7, 8, 9). Since it may take several serial passages before the agent is present in sufficient concentration to carry out appropriate tests to establish its identity, the recovery and identification of a viral agent is a procedure which may require a considerable period of time when compared to that necessary with most bacteria. It is therefore desirable to undertake such studies only following a discussion between the laboratory and clinical departments. The selection of the tissue or fluid from which to attempt the recovery of a virus obviously varies with each disease and several representative ones will be discussed later. As a general rule, a higher percentage of positive results will be obtained if such specimens are restricted to those collected during the acute phase of the patient's illness. It should be remembered that only positive findings are significant, and that failure to recover a virus does not rule out infection by such an agent.

When they are possible, *serological tests* are usually less time consuming and hence more desirable for diagnostic purposes (10). Because of the minute size of most viruses, the bacterial type of *agglutination test* is not practicable. Neither are *precipitin tests* at present of more than academic interest. However, it has been recently discovered that the red cells of chickens and certain other fowls and mammals are agglutinated in the presence of influenza A and B (11), mumps (12) and several other viruses (13, 14), and that this agglutination may be inhibited by specific antibodies which appear in the serum of convalescent patients. These observations form the basis of the so-called "*Agglutination-Inhibition*" (A-I) test (15) which is the simplest and most rapid of the several virus serology techniques. It is now used chiefly to detect and to type clinical cases of influenza (16). Like all other virus serology, in order that the results may be properly interpreted, a serum obtained during the acute phase of the patient's illness should be compared in the same test with one obtained during the convalescent phase. *Complement fixation (CF) tests* are also now available for influenza (17), psittacosis (18), lymphopathia venereum (19), mumps (20, 21), lymphocytic choriomeningitis (22) and several of the encephalitis producing viruses (23). For these tests it is important that all sera be collected aseptically and be stored in the cold lest they become anticomplementary and so react nonspecifically with complement. If prolonged storage is contemplated, the sera should be frozen, for even at refrigerator temperature, complement fixing antibodies slowly deteriorate. The *neutralization or protection test* is a classical procedure in virology (4, 24). Unlike the A-I or CF tests which are *in vitro* examinations, it involves the use of animals. In its essence it consists of mixing an active strain of a known virus with the patient's serum, inoculating susceptible animals and observing the degree of protection afforded by the patient's serum to these animals. Again, differences of behavior between sera obtained during the acute and convalescent phases are compared. For this purpose it is desirable to have specimens from the first, third and eighth weeks of the patient's illness.



*Histopathological* examinations supplement all virus studies, but they are of particular assistance in diagnosis when specific lesions or inclusions can be demonstrated (3). The so-called "*inclusion bodies*" may be found in either the cytoplasm or nuclei of infected cells and are either visible evidence of the effect of the intracellular growth of the virus or, as in the instance of elementary bodies, actual virus particles or clusters of such particles (2). Direct visualization of these and several other viruses is possible with the aid of the electron microscope (25, 26, 27). Unfortunately, this procedure is not yet applicable to diagnosis of virus diseases.

*Application of the technics of virology to the diagnosis of some specific diseases.* In Table I there are listed a number of virus diseases selected to illustrate more specifically how, when properly employed, the aforementioned technics may aid the clinician in arriving at an etiological diagnosis.

When throat washings or garglings are available from a patient acutely ill because of influenza, they may be mixed with penicillin (28) and inoculated directly into chick embryos (29). In this manner it may be possible to isolate and identify an influenza virus within 2 to 8 days from the time the patient is first seen and clinical suspicion of influenza is aroused. However, a simpler method of confirming this impression and one which at the same time usually yields reliable information as to the type of influenza within 10-14 days is to study in an A-I test acute and convalescent phase sera for their capacity to inhibit agglutination by type A or B strains of influenza virus. If the patient had actually been ill because of influenza, a 4-fold or greater rise in antibody against the infecting type is usually found during convalescence (15, 16).

From the sputum or lungs of a patient thought to have ornithosis or psittacosis, the virus may be isolated by the inoculation of chick embryos or mice (30). It may be identified as a member of the ornithosis-lymphopathia venereum group of viruses by the demonstration of elementary bodies in properly stained smears from infected animal or chick tissues. More exact identification of the agent requires serological tests with specific immune sera prepared in chickens (31) or a study of its comparative pathogenicity for several laboratory animals (32). In general, the appearance in the patient's serum during convalescence of CF antibodies for the ornithosis-lymphopathia venereum group of viruses is sufficient to confirm the clinical impression. Because of antigenic similarities, it is possible to use a commercially available lymphopathia venereum virus antigen for this test (19). Patient's infected with one of these viruses will often also give a positive Frei test. However, the CF test is a more sensitive reactions.

The etiological agent in the majority of instances of primary atypical pneumonia is still unknown (33, 34). Consequently, there are no specific laboratory tests. There are, however, two non-specific and incompletely understood, reactions which appear in approximately 40-60 per cent of the patients seen with this disease in this country. When present, they are valuable aids to diagnosis. They are the appearance in convalescence of high titers of cold red blood cell agglutinins (35) and agglutinins for the indifferent MG streptococcus (36).

These reactions are independent of each other and reflect different antibodies, although both may appear in the same patient (36, 37). When blood is collected for a cold agglutination test, it is important that the serum be separated while the specimen is still at body or room temperature.

Fortunately, rabies in which the mortality is still 100 per cent is a rare human disease in this part of the world. It is included in this list because the diagnosis can be made by the demonstration of the characteristic inclusion or Negri bodies in the cytoplasm of the infected brain cells. The diagnosis can be confirmed

TABLE I  
*Practical laboratory aids to diagnosis of some representative viral diseases*

DISEASE	AIDS TO CLINICAL DIAGNOSIS				AIDS TO POST-MORTEM DIAGNOSIS		
	Isolation of virus from:	Detection of antibodies			Specific lesions	Isolation of virus from:	Laboratory animals of choice
		CF	Neut.	Others			
Influenza	throat washings	+	+	A-1		lungs	chick embryo
Psittacosis (Ornithosis)	sputum	+	+	skin test	elementary bodies	lungs	chick embryo or mouse
Primary atypical pneumonia				Cold aggl. MG strep. aggl.			
Rabies					negri bodies	brain	mouse
Poliomyelitis	stool and nasopharynx				anterior horn cell degeneration	brain and cord	monkey
Eastern equine encephalitis		+	+			brain	mouse
St. Louis encephalitis		+	+			brain	mouse
Lymphocytic choriomeningitis	spinal fluid and blood	+	+			brain	mouse or guinea pig
Mumps	saliva and spinal fluid	+	+	A-I, skin test			chick embryo
Herpes simplex	blister fluid and ulcer base		+		intranuclear inclusions	brain	rabbit, chick embryo or mouse

by passage of an emulsion of brain tissue to mice to produce a fatal encephalitis with pathological findings similar to those seen in man and other animals (38).

Poliomyelitis is another disease in which the pathologist can best help the clinician by demonstrating specific lesions. The isolation of the poliomyelitis virus almost always requires the use of monkeys and so for obvious reasons is not practical on a clinical level. Since most adults seem to have circulating antibodies for this virus, there are no reliable serological tests for this disease (10). However, when presented with a patient with clinically atypical poliomyelitis, the investigator in his laboratory can assist in arriving at a correct diagnosis

by ruling out infection by one of several of the other recognized neurotropic viruses.

Eastern equine encephalomyelitis and St. Louis encephalitis may be considered together. Isolation of the virus is very rare except from brain tissue obtained at post-mortem examination. Both CF and neutralization tests are reliable indicators during life of past infection. The antibodies detected by the neutralization test usually appear slightly earlier than the CF antibodies and persist much longer (23). Because of their short duration and the fact that they are not elicited by vaccination, the detection of specific CF antibodies is usually indicative of recent infection. However, as in all virus serology, acute and convalescent phase sera should be compared.

The lymphocytic choriomeningitis virus may give rise to a great variety of

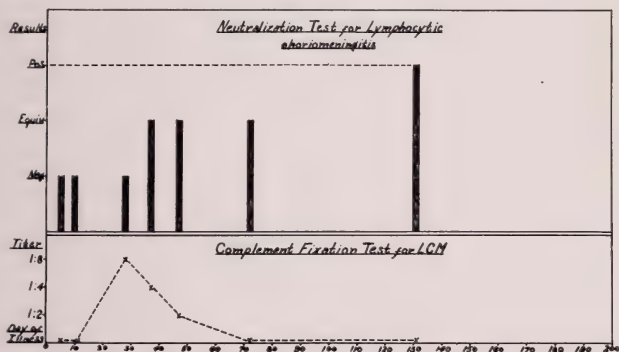


CHART I. Development of Antibodies against Lymphocytic Choriomeningitis

P. L.—Onset of illness—10 Nov., 1944; virus isolated from blood and C. S. F. obtained—15 Nov., 1944

clinical patterns including, in addition to the familiar meningitis and encephalitis, "flu" and pneumonia (39). The virus can be recovered from the spinal fluid or blood during the acute phase of illness by inoculating guinea pigs or mice. Both CF and neutralizing antibodies appear during convalescence, but unlike what occurs in patients recovering from eastern equine or St. Louis encephalitis, the CF antibodies appear much earlier (23). The value of doing both CF and neutralization tests in this disease is demonstrated in Chart I which summarizes these tests done on sera from a patient studied in detail about two years ago. Although we had isolated a strain of lymphocytic choriomeningitis virus from the blood and spinal fluid of this patient in our laboratory, it was not until sometime between the 72nd and 130th day, which is much later than usual, that a positive neutralization test for this virus could be demonstrated with the

patient's serum. By this time the CF test had already become negative. The relatively short time that CF antibodies were present is noteworthy.

The virus of mumps may be isolated from saliva and spinal fluid of patients by direct inoculation into chick embryos (40). The demonstration of the development of mumps CF antibody during convalescence has proved especially valuable in instances of mumps without parotitis (20). A skin test with mumps virus has also been described which is useful in epidemiological surveys (41).

In addition to its etiological role in the common fever blister, the herpes simplex virus has recently been incriminated in certain instances of stomatitis (42), keratoconjunctivitis (43), dermatitis (44), meningitis (45) and encephalitis (46). It can be recovered from a variety of tissues by inoculation onto scarified rabbit

TABLE II

*Some virus diseases and probable virus diseases of man grouped according to present availability of practical laboratory aids to diagnosis*

	DISEASES PRIMARILY OF			
	Respiratory tract	Nervous system	Skin	Other systems
A Specific laboratory aids are available for:	Psittacosis (ornithosis) Influenza A and B	Lymphocytic choriomeningitis Eastern equine encephalitis Western equine encephalitis St. Louis encephalitis Jap B encephalitis Rabies	Herpes simplex Vaccinia Smallpox Molluscum Contagiosum	Mumps Lymphopathia venereum Yellow fever Inclusion blennorrhoea Trachoma
(B) Non-specific laboratory aids are available for:	Primary atypical pneumonia			Infectious mononucleosis
(C) No practical laboratory aids to specific diagnosis are yet available for:	Common cold	Poliomyelitis Guillian Barré syndrome Post-infectious encephalitis Post-vaccination encephalitis Landry's ascending paralysis	Herpes zoster Stevens-Johnson's disease Warts	Infectious hepatitis Epidemic diarrhea Measles German measles Chicken pox

cornea, into mouse brains or onto the chorioallantoic membranes of chick embryos (47). It produces characteristic intranuclear acidophilic inclusion bodies in infected cells. Because of the almost universal finding of antibodies to this virus in the sera of adults, serological tests are of doubtful clinical value except in the very young.

To summarize the usefulness as well as the limitations of laboratory studies in the diagnosis of virus diseases, Table II has been prepared. In it a number of the more frequently encountered clinical disease entities of virus or probable virus etiology are grouped according to the present availability of practical laboratory diagnostic aids. Although these are still limited in scope, their proper employment will do much to further a better understanding of virus diseases and their management.

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## COMPARISON OF PNEUMOENCEPHALOGRAPHY AND ELECTRO- ENCEPHALOGRAPHY IN BRAIN TUMORS\*

BENNO SCHLESINGER, M.D., AND HANS STRAUSS, M.D.

*From the Neurosurgical Service and the Neurological Service of The Mount Sinai  
Hospital, New York City*

A brief summary outlining the principles of pneumoencephalography and electroencephalography is deemed advisable before entering into a discussion of their comparative results in the diagnosis and localization of intracranial tumors.

In pneumoencephalography<sup>1</sup> a gaseous contrast medium, usually air, is injected either into the subarachnoid space, from where it may enter the cerebral ventricles, or directly into the lateral ventricles, from where it may pass into some of the subarachnoid space, thus permitting the visualization of both systems. Only on rare occasions is the tumor completely surrounded by air and visualized as such radiographically. In all other instances the presence and site of an expanding lesion must be determined by an alteration in the size, shape and position of the cerebrospinal fluid spaces, usually the distorted or displaced ventricles.

The electroencephalogram is a record of electrical potentials originating in the brain and recorded by means of electrodes placed upon the scalp and nearby surfaces, e.g. the ear lobes or the mastoid processes. It is a test of cerebral function and does not give any direct information as to the morphologic condition of the brain. However, from the type of abnormality certain conclusions can be drawn as to the nature of the underlying pathologic process as well as to its location. It is significant to recall that in cases of expanding lesions of the hemispheres the abnormal potentials recorded do not originate in the tumor but in the surrounding tissue, the metabolism of which is disturbed by the tumor. As a rule, in tumors of the cerebral lobes, the disturbance is greatest in, or even entirely confined to the tissue immediately adjacent to the tumor. This produces a focal abnormality in the electroencephalogram indicating the site of the neoplasm. Expanding lesions of a non-neoplastic character, such as abscesses, subdural hematomas and others may induce a similar type of record, just as their pneumoencephalograms may be similar to those of truly neoplastic lesions. Fortunately cerebrovascular disease is only rarely associated with the types of electroencephalographic records produced most frequently by hemispheric tumors. Neoplasms of the posterior fossa, including those of the cerebellum, may cause abnormalities in the electroencephalogram by exerting direct pressure upward upon the occipital lobes, or indirectly by disturbance of cortical function consequent to an internal hydrocephalus with pressure effects upon the cortex

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<sup>1</sup> Pneumoencephalography in this paper denotes pneumography by the lumbar, cisternal or ventricular route.

or upon pace makers of electrical cortical function in the region of the third ventricle. These tumors do not induce any focal abnormalities at their site. Therefore, one cannot expect the diagnosis of posterior fossa tumor to be made from the electroencephalogram. These introductory remarks should make it clear that primary observations do not by themselves establish the diagnosis but that such a diagnosis has to be based upon the *interpretation* of findings, irrespective of which of the two methods is considered.

Our material consists of 116 cases of intracranial tumors. All were subjected to electroencephalography and pneumoencephalography and all were verified by biopsy or autopsy. Twenty-seven cases were infratentorial, suprasellar or intraventricular tumors. In none of these cases did the electroencephalogram localize the lesion. The records were normal in 10 cases and in the remaining 17 they showed changes that were not characteristic of any one particular localization. In all these 27 cases the PEG proved to be the superior method since it localized the lesion in every instance.

TABLE I

*Positive (+) and negative (-) results of pneumoencephalography (PEG) and electroencephalography (EEG) in intracranial tumors of various localizations*

LOCALIZATION OF TUMORS	TOTAL NUMBER	PEG+ EEG+	PEG- EEG-	PEG+ EEG-	PEG- EEG+
Suprasellar, intraventricular and infratentorial.....	27	0	0	27	0
Basal ganglia and thalamus opticus.....	4	0	1	3	0
Hemisphere lobes.....	81	40 (49%)	4 (5%)	30 (37%)	9 (9%)
Total.....	112	40	5 (4.5%)	60	7

There were four cases of tumor of the basal ganglia and the optic thalamus. In one case the diagnosis could not be made either by the PEG or EEG. In the remaining three cases, the PEG localized the tumor correctly while the EEG was correct only as to the laterality but not as to the exact site of the lesion.

There were 81 cases of tumors of the cerebral lobes. In 47, or about 60 per cent, an exact electroencephalographic diagnosis could be made, while in the remaining 40 per cent the EEG was either normal or did not localize the lesion correctly. The PEG gave correct results in 70 or approximately 86 per cent of these cases and failed in 11 cases or approximately 14 per cent. In brain tumors of this group the PEG is, therefore, more successful in 25 per cent of the cases than the EEG. This does not imply that the results obtained by pneumoencephalography are in each case superior to those obtained by electroencephalography. In fact, our material shows seven cases in which the EEG gave the correct and desired information while the PEG failed (see Table I<sup>2</sup>).

<sup>2</sup> Four cases with multiple tumors are omitted from Table I since the exact localization was not determined.

In only 4.5 per cent of the total material neither pneumoencephalography nor electroencephalography was of assistance.

Thus far it has been shown:

1. Electroencephalography cannot localize a tumor in the posterior fossa, the suprasellar region, the third or lateral ventricles, while pneumoencephalography gives positive results in all these cases.

2. The results of electroencephalography are not as good as those of pneumoencephalography in the localization of tumors of the cerebral hemispheres, although some of these tumors were diagnosed correctly by the EEG while the PEG failed.

These two statements are based on cases in which both pneumoencephalography and electroencephalography were performed. They do not, therefore, represent our total material of brain tumors but merely a selected group. There were 142 cases of intracranial tumors in which EEG's were taken but which never had PEG studies. One of the obvious reasons for not performing a PEG was that the localization seemed well established without this test. Therefore, pneumoencephalograms would be performed in cases in which there was a discrepancy between the clinical and laboratory findings, including the EEG. In consequence, the group described here must of necessity contain more cases of failure of the EEG than the general material.

Our total material of tumors of the lobes of the cerebral hemispheres shows a correct localization in 70 per cent. The results are not as satisfactory in the meningiomatous tumors as in the gliogenous and metastatic tumors where the correct localization was made in 72 per cent, but even this latter figure does not equal the accuracy of the PEG.

In comparing the two methods, one should not consider only their results. One must also consider the degree of discomfort and hazard each procedure entails. In an electroencephalographic examination hazards and discomfort are negligible. In pneumoencephalography discomfort may be considerable and some hazards are difficult to avoid. On the other hand, one should not overlook the fact that the examiner, on whom the final responsibility rests, and who performs the pneumoencephalogram by the lumbar, cysternal or ventricular route, deliberately chooses the lesser evil. The greater evil is a misdirected surgical exploration with the disheartening experience of an early postoperative fatality. The least, both the patient and the surgeon can expect from an inaccurately placed bone flap, are a difficult exposure and an incomplete removal of the lesion, due in part to difficulties in hemostasis, which in turn cause traumatization of nervous tissue. Electroencephalography, therefore, should be performed in every case of brain tumor suspect, even if the probability of a brain tumor being present is remote, whereas pneumoencephalography should be limited to those cases in which the presence of such a lesion is suggested by the clinical examination but in which neither the electroencephalographic nor any other laboratory examination provides the surgeon with sufficiently accurate diagnostic data.

The results reported in this paper are those of the various services of The

Mount Sinai Hospital engaged in the task of brain tumor diagnosis. Other hospitals may compile their material in a similar manner, but they will in all likelihood arrive at somewhat different percentages since a very important personal factor governs the interpretation of both the EEG and the PEG. This personal factor is fully appreciated by those who perform the examinations and evaluate the diagnostic data. They know that no single diagnostic method such as pneumoencephalography or electroencephalography will ever replace the one diagnostic procedure, namely the careful clinical examination by the experienced neurologist and neurosurgeon, upon which any other procedure and decision would finally rest.



## "BENIGN" (IDIOPATHIC) BRONCHIAL BLEEDING

### REPORT OF A CASE<sup>1</sup>

ARTHUR R. SOHVAL, M.D.

*From the First Medical Service, The Mount Sinai Hospital*

It has long been recognized that hemoptysis, single or recurrent, may be the result of bleeding from the bronchial mucous membrane in the absence of any detectable lesion in the bronchi or any constitutional disease. Prolonged follow-up observation of these patients indicates that the course is benign; for this reason such hemoptysis has been designated "benign" bronchial bleeding. However, "idiopathic" is a preferable term since many diseases characterized by hemoptysis are also benign in the sense that they are not malignant anatomically. Wessler aroused interest in this group of patients by his demonstration that benign bronchial bleeding is relatively common.

It should be emphasized that appropriate clinical and laboratory examinations must be performed to exclude other causes of hemoptysis. In addition to obviously recognizable diseases of the bronchi, lungs, cardiovascular and hematopoietic systems, bronchiectasis without previous clinical evidence may be an etiologic factor. It is often necessary, as in the case reported, to study complete bronchograms made with lipiodol in order to eliminate this possibility. Further, the condition known as hereditary telangiectasia must be ruled out by careful scrutiny of the skin and accessible mucous membranes.

#### CASE REPORT

*History.* (Adm. #458088) M. V., an engineer, aged 42 years, was admitted to the hospital on June 10, 1940, complaining of hemoptysis for the previous two and one-half weeks. He stated that he first expectorated blood about twenty years ago, some weeks after recovering from pneumonia. Since then he has been susceptible to colds and has a "smoker's cough", characterized by slight morning cough. Six weeks prior to admission, he developed a "chest cold" with yellowish sputum and "music" in the right chest. This cold had just disappeared at the time he coughed up some blood-streaked sputum about 18 days before admission. The next morning he cleared his throat and brought up a mouthful of fresh blood. Later, while eating, he felt an uneasy sensation in his throat, followed by bleeding, which was so profuse that he had to bend over a sink to let the blood run out and to keep from choking. This lasted about five minutes. For the six days before admission, he had been coughing up thick, dark clots (about 1 teaspoonful) every morning. Just before this was expectorated, he felt as if there was something in his throat. One day he brought up a worm-like clot about one inch long, along with some fresh blood.

*Examination.* There were no significant abnormalities. Blood pressure was 138 systolic, 78 diastolic. Complete blood count, tourniquet test, bleeding and coagulation time, and clot retraction were normal. X-ray examination of the chest showed no abnormality in the lungs. A sputum examination disclosed no acid-fast bacilli. Examination of the upper respiratory tract revealed no source of bleeding.

*Course.* Bronchoscopy, performed three days after admission, revealed some thick, blackish mucoid secretion in the bronchi of the right lower lobe. Just below the middle

<sup>1</sup> Presented as part of a Symposium on Hemoptysis at the Monthly Conference of the Thoracic Group, May 7, 1945.

lobe bronchus, on the left wall of the lower lobe bronchus, there was a bleeding point in the mucosa. Another bleeding point was seen in the mucosa of the left lower lobe bronchus, just below the upper lobe bronchus orifice. The mucosa itself otherwise appeared normal. No evidence of new growth was seen.

Because of the history of recurrent respiratory tract infections, the chest was again examined roentgenographically after the injection of iodized oil into the bronchial tree. All branches of both lungs were demonstrated to be well filled, and showed no abnormality. There was no bleeding or cough during the nine day hospital stay, nor was there a recurrence when the patient was last examined in the Follow-up Clinic six years later.

#### COMMENT

As a general rule, idiopathic bronchial bleeding starts and stops quite suddenly and prompt expectoration accounts for the bright red, fluid blood usually observed (Wessler). However, this case demonstrates the fact that at times the blood may assume a dark red color and even become clotted if it has remained in the bronchi long enough before expectoration. The worm-like clot expectorated by this patient indicates that coagulation occurred in a segment of a bronchus and points to the explanation of certain complications occasionally encountered in these patients. Failure to expectorate such a clot in a small bronchus may cause obstruction and partial pulmonary atelectasis. The resulting roentgen shadow may be misinterpreted as an infiltration and a true differentiation can sometimes be made only by reexamination after a week or two. Secondary infection of the retained blood clot may produce the clinical picture of bronchopneumonia.

Although the cause of idiopathic bronchial bleeding is unknown, the frequent occurrence of antecedent severe exertion, emotional excitement or upper respiratory tract infection suggests that these may be significant precipitating factors. Both episodes of bleeding in this case, the first twenty years previously, followed a respiratory infection.

The bleeding points noted by the bronchoscopist in this case correspond to the bronchoscopic findings in almost one half of the cases observed in this hospital. These findings consist of a bronchial mucous membrane which was so friable or fragile that mere contact with a sponge or with the lip of the bronchoscope induced bleeding. In some instances, solitary or multiple bleeding points were described without evidence of excessive fragility of the mucous membrane.

It is difficult to evaluate the significance of these bronchoscopic findings, especially in view of the fact that the bronchial mucous membrane is acknowledged to be more delicate than other mucous membranes, and consequently is more apt to bleed when traumatized during instrumentation. This may be due to the fact that it covers rigid cartilage and there is no "give" on pressure. This difficulty is further enhanced when one considers the variable factor of how intensely the patient may be straining during the bronchoscopy. It is not at all impossible that severe straining may engorge the capillaries of the bronchial mucous membrane (as it does in the face) to such an extent that it may bleed spontaneously, or on mere contact with a sponge or the bronchoscope itself. Unfortunately no data are available concerning the effect of bronchoscopy on

blood pressure and particularly on the pressure of the vessels in the bronchi. Furthermore, we must be cognizant of the personal factor in the operator himself who has been given the task of determining the cause of bronchial bleeding in a patient whose lungs and cardiovascular system are apparently normal. Unless he encounters an obvious bronchial lesion, he is naturally inclined to extend the search and pay attention to minute details in the appearance and reaction of the mucous membrane. This may account for the fact that other bronchoscopists here and elsewhere have not observed or commented upon this condition of excessive friability. It may also explain why this finding is observed almost exclusively in otherwise negative bronchoscopic reports and has apparently not been noted or described in the rather large number of bronchoscopic examinations in which bronchial neoplasm or foreign body was demonstrated.

#### SUMMARY

A case is reported in which hemoptysis was due to bleeding from an apparently normal bronchial mucous membrane. There was no evidence of pulmonary, cardiac, hypertensive, vascular or hemic disease.

#### REFERENCE

WESSLER H.: Notes on Hemoptysis. J. Mt. Sinai Hosp., 7: 548, 1941.

# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 19

### LEUKEMIA

Few diseases illustrate the need of a biological interpretation more than the leukemias. The conventional static study of these diseases has resulted in a bewildering classification and terminology, largely because phases have been demarcated as distinct disease entities. This is due in the largest measure to the insufficient realization that the cells of the hematopoietic system are endowed with potentialities for change in morphology and function that are not even necessarily synonymous with maturation. Indeed, such a change more often represents a reversion to an embryonic status. The issue has been further confused because the definition of certain disease mechanisms, such as "inflammation," "hyperplasia" and "neoplasia" has received a wide range of interpretations. Until these mechanisms are better understood, it would simplify matters considerably to depend upon observations of clinical and morphological transitions and to note their sequences and correlations. A study of very early cases is particularly desirable.

One of the consequences of the various interpretations has been the lack of a sharp definition as to what is meant by the term "leukemia." A clinical and morphological correlation is not always present. In other words, there may be a greater or lesser percentage of immature leucocytes in the blood without leukemic infiltrations in the organ and on the other hand, there may be the characteristic leukemic morphological changes (pseudoleukemia) without either an increase in the number or the presence of immature leucocytes in the blood (aleukemia). Nevertheless, the aleukemias very often later develop the characteristic hematological changes. This does not imply a change in the nature of the disease, but only a biological change. Furthermore, as the result of secondary changes in the hematopoietic organs, the true nature is often clinically masked by a superimposed clinical expression, such as granulocytopenia, hemolytic anemia, aplastic (myelophthisic) anemia, thrombocytopenic purpura, etc. and it is only by a study of the tissues, especially the bone marrow, that the true nature of the disease is disclosed. These clinical and morphological shifts render the diagnosis an occasionally difficult one, and it is only by a mutual study from both points of view and especially by the observation of transitions, both clinical and morphological, that the true nature of leukemia can be established. Even under such circumstances, the diagnosis is sometimes doubtful.

<sup>1</sup> This is the nineteenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the *Journal of The Mount Sinai Hospital*. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

*Chronic lymphatic leukemia.* Being an insidious disease, the earliest phase in man is not known. The closest approach was a case reported by Stasney and Downey (1) which eventually developed into a subacute lymphatic leukemia. Three successive biopsies of lymph nodes were performed. In the early stage the node showed a "hyperplasia" of the reticulum cells. At the same time, the peripheral blood showed cells of the "reticulo-endothelial" type but with a nucleus of lymphocytic pattern. The later biopsy presented a dense mass of immature lymphocytes in the medullary region of the lymph node. The "reticulo-endothelial cells" disappeared from the blood and only immature lymphocytes were present. In their view, the case reveals the embryonic potency of the syncytial reticulum cells. If mouse leukemia is identical with human leukemia, the findings of Stasney and Downey are precisely duplicated by Potter, Victor and Ward (2) who found that the early phase of lymphatic leukemia in the mouse is a "hyperplasia" of the reticulum of the medullary tissue of the lymph nodes and the perivascular regions of the liver. These observations coupled by clinical experience already demonstrates that "aleukemic" leukemia is not a separate disease but represents a transition to the subleukemic and finally to the leukemic phase. As Opitz (3) observes, it depends upon how long the patient lives. It is true that many leukemic patients die even in the aleukemic stages, but in such death is often the result of factors unconnected with the fullest fruition of the disease.

The biology of chronic lymphatic leukemia is closely related to the potentialities of the lymphocytes and especially toward neoplasia. There has been much debate ever since Babes (4) broached this possibility and there are certain transitions that suggest such a neoplastic origin from the point of view of aggressiveness, cell atypicism and metastatic invasion. We refer especially to the cases in which the earliest manifestation of the disease is a localized growth of the lymph nodes that has been termed "leukosarcoma" (Sternberg) "lymphosarcoma" (Kundrat), "lymphocytoma", "reticulum cell sarcoma" and "giant follicular lymphadenopathy." These, with or without leukemic infiltrations have been grouped under such terms as "lymphadenosis" or "lymphomatosis." The reports of a leukemic blood picture following such an event are common enough (5, 6, 7, 8, 9, 10, 11). The primary tumor may be in the mediastinum, intestinal tract, regional lymph nodes, skin, bone, etc. The question arises whether these cases represent true transitions of sarcoma into leukemia or a malady distinct from leukemia. The latter view is held by Richter (11) Isaacs (5) on morphological grounds, since the hematic cells in their cases were not true lymphocytes, but had the characteristics of "lymphosarcoma" cells. To their view, despite the presence of true "leukemic" infiltration in the liver and spleen, these represent cases of lymphosarcoma in which the neoplasm has broken into the blood vessels and has spread throughout the organs by colonization. In this interpretation, the "leukosarcoma" which has no distinctive morphology must be differentiated from the other forms of sarcoma previously mentioned. This interpretation however does not take into consideration the fact that the cell morphology is not absolute and true to type but relative, and



depends, as Klemperer (12) emphasizes, upon the potentialities of the cytoplasmic reticulum of the myeloid and lymphoid tissue, which, under various abnormal conditions, reverts to its embryonic functions. One of these functions is the development of cells along hematic lines and the type of cell will vary according to the degree of differentiation. This has been shown in the cells of fixed tissue. Banti (13), Klima (14) and Opitz (3) call attention to the frequently different morphology in the biopsy as compared to the autopsy in lymphatic leukemia. Ehrlich and Gerber (15) describe three dominant types of cells in lymphosarcoma—small lymphocytic, large lymphocytic and intermediate—but admit that they are usually mixed and that they display transitions from biopsy to autopsy. Nevertheless they believe that lymphosarcoma in their sense differs from the “lymphadenomas” in certain particulars, especially in their regional origin, in the tendency to metastatic deposits, and in the presence of leukemic cells in the blood stream. They also showed that the amount of fibrillar reticulum which is a derivation of the cells varied in specimens removed at different times. Klemperer (12) illustrates these transformations from specimens removed at different stages and he shows changes from a “lymphosarcoma” to a “reticulum celled” sarcoma and reversely. Even the giant follicular lymphoblastoma eventually transforms into either “lymphosarcoma” or “reticulum celled” sarcoma, and occasionally even into lymphatic leukemia (7, 8, 10). This potentiality of the fixed cytoplasmic lymphoid reticulum accounts for the varying interpretations of these types. In the last analysis they represent mutations and thus far the attempts to subdivide them up into well defined species has only confused the issue and has introduced a bewildering terminology. What factor or factors influence the change in one direction or the other are not entirely clear. One of the factors, as we shall point out shortly, is radiation.

This change applies not only to the fixed lymphoid reticulum but to the free cells that have entered the circulation. We have already referred to Stasney and Downey's observation that the hematogenous cells changed from a “reticuloendothelial” to pure lymphoid type in the later stages. Wiseman (9) reports normal lymphocytes mixed with “neoplastic” cells within the blood. Graetz (17) reports cases of leukosarcoma in which in the early phases small lymphocytes were the dominant blood cells, while in the terminal phases they were large.

The attempt to differentiate types of lymphatic leukemia from the morphological study of the cells of the lymphoid type in the blood alone must be viewed with reserve.

The problem now arises whether this type of lymphatic leukemia, which begins at a localized swelling of the lymphoid reticulum and after passing through an aleukemic phase into a leukemic, is a different disease than the conventional type which is presumed to begin in an autochthonous form with generalized lymph node swelling. The advocates of this dichotomy point to the different course, the different morphology of lymphoid cells both in the tissues and in the blood, the comparative absence of localized tumor formation and splenomegaly and lymphadenopathy in the cases that begin with “leukosarcoma” and the infrequency of metastatic deposits in the conventional type of lymphatic leukemia.

On a critical appraisal it seems to us that these differences are more specious than real. In the first place, neither type is biologically pure since there is abundant evidence that more or less crossing of these differentials is extremely frequent; second, as we have tried to show, there is no sharp distinction in the morphology, since mutations are exceedingly common; third, the differences are based on the assumption that in the conventional type of leukemia the characteristics began as such and did not pass through a developmental stage. We have already cited the important observation of Stasney and Downey, that lymphatic leukemia begins from a small focus in the pulp cords of the medulla which spreads peripherally throughout the lymph node and that it passes from an aleukemic phase to the leukemic termination. This is precisely comparable to the type of leukemia which begins as a "leukosarcoma" except on a smaller scale. Furthermore, if experimental mouse lymphatic leukemia may be regarded as the analogue of that in man, the identity of the generalized lymphatic leukemia with the leukosarcomatous variety seems perfect. Furth, Siebold and Rathbone (18) found that after intravenous injection of certain strains of living leukemic cells they were able to obtain in all instances a lymphatic leukemia which was preceded by a transient aleukemic stage. By subcutaneous inoculation, they usually produced a leukosarcoma with metastases and in rare instances lymphatic leukemia without tumor formation. Furth and Kahn (19) could inoculate mice with leukemia with a single living cell. Furth and his coworkers conclude that lymphosarcoma, "leukosarcoma" aleukemic lymphomatosis, leukemic lymphomatosis (lymphatic leukemia) are identical and represent different manifestations of the same disease. Richter and Mac Dowell (20) and Webster (6) are of the same opinion. Certainly when both types have attained their fruition, they are both clinically and morphologically indistinguishable.

One of the factors that determine the transition from leukosarcoma to lymphatic leukemia is undoubtedly x-ray therapy. This sequence has been noted by a number of observers (21, 22). Furth and his coworkers created a greater susceptibility in their animals by subjecting them previously to x-rays. This has been confirmed by others (21, 22). This no doubt accounts for the fact that the incidence of lymphatic leukemia in radiologists is ten times greater than in non-radiological physicians (23).

The biology of lymphatic leukemia, as we have outlined it, is paralleled in other types of leukemia. This will be discussed shortly.

There are other mutations in lymphatic leukemia that may complicate the clinical expression. It is sometimes difficult to determine whether these mutations are initial or terminal phenomena since the malady had already attained considerable progress before clinical manifestations arose. We refer to the various types of anemia and to the changes in the granulocytes and platelets that have been frequently noted in association with lymphatic leukemia. The anemia is usually normochromic and rarely hyperchromic. Although the blood picture of the hyperchromic variety simulates pernicious anemia and the combination has been termed "leukanemia," a valid pernicious anemia with complete achlorhydria has never been reported as associated with lymphatic leukemia. A

"leukanemia" is therefore not a separate entity. The anemia may be accompanied by a thrombocytopenia (9, 14, 24) or it may resemble the aplastic or myelophthisic type (9); exceptionally it may resemble a hemolytic anemia, which is sometimes the earliest manifestation (24, 25, 26, 27). When these mutations occur early the diagnosis may only be cleared by bone marrow puncture. We have observed a number of such instances. Lymphatic leukemia is sometimes associated with the clinical and morphological manifestations of a granulocytopenia (9, 24) and occasionally unripe granulocytes may appear in the blood (28). All these mutations are in some measure due to invasion of the bone marrow by the leukemic process. The presence of immature granulocytes in the blood may be accounted for by a compensating extramedullary hematopoiesis, comparable to that which occurs in cases of extensive osseous metastases. The various stimuli that set forth the remaining types of mutations are obscure. In how far x-ray therapy leads to these mutations has not been entirely clarified.

*Myeloid leukemia.* The earliest lesion of myeloid leukemia is entirely unknown, the reason being that it is an insidious disease and does not become clinically manifest until the lesions are fairly advanced. Although experimental myeloid leukemia with living leukemic cells in certain strains of mice (29, 30) and in fowl by a filterable virus (29) can be fairly consistently produced by the same procedure and with identical results as in experimental lymphatic leukemia, the earliest phases are not reported. It is possible that the cases of "aleukemic myelosis" (32) or "aleukemic reticulosis" (33) represent, if not the earliest, at least an early stage. That chronic myeloid leukemia may also pass through an aleukemic phase has been shown by King (34). Chronic myeloid leukemia does not follow the acute form since clinically, anatomically and hematologically they appear to be entirely different diseases. Since the potentialities for differentiation of the hematocytoblast (Ferrata) which is generally regarded as the progenitor of the myeloid series is greater, morphologically speaking, than that of the lymphoid reticulum, a wider range and atypicism of cells in both fixed tissue and in the blood are noted in myeloid leukemia than in lymphatic leukemia. Both tissues and blood contain a wide variety of cells of the myeloid series, from the unripe to the mature form, including eosinophiles and basophiles; and the longer the disease lasts the more immature the cell, so that eventually instead of myelocytes, the predominant cell type is the myeloblast. In acute myelogenous leukemia, on the other hand, the potentialities for differentiation are almost lost, since there are few or no intermediary forms between the myeloblasts of the blood and the mature segmented types. There is no conclusive evidence that lymphatic leukemia is converted into myeloid leukemia. We have already noted that cells of the myeloid group may pass into the blood from extramedullary hematopoiesis in lymphatic leukemia, but this does not constitute a transformation, nor is there any positive support for the transition of myeloid into lymphatic leukemia. Most of such reports date before the differentiation between lymphocytes and myeloblasts was rendered possible.

In other respects the evolution of myeloid leukemia parallels that of lymphatic leukemia closely. Tumors of the blastomatous type have been described, al-

though they are not nearly as frequent as in leukosarcoma. The most familiar are the chloromata arising from the bone or periosteum. These are always associated with acute myeloblastic leukemia. Cooke (35) reported nine cases of acute leukemia in children associated with a large mediastinal sarcomatous mass. In four, this mass preceded a rather sudden invasion of the blood with leukemic cells, despite the disappearance or lessening of the size of the mass by x-ray. Such mediastinal masses were present in two of forty-eight cases of myelogenous leukemia in adults reported by Kirklen and Hefke (36). Tumors of other parts of tissue associated with "myelosarcoma" have been reported by others (37, 38, 39). The blood invasion sometimes follows x-ray treatment, or without it.

Hematological mutations similar to those described in lymphatic leukemia have been described in myeloid leukemia. Hemolytic icterus has been reported by Brill (40), Boe (27) and Klima (14), thrombocytopenia and granulocytopenia by Klima and Seyfried (24) and Opitz (3). Sternal puncture again is decisive. The stimuli that cause these mutations is not definitely known. As in lymphatic leukemia, radiation may be a factor.

*The transition of polycythemia vera to myeloid leukemia.* The term "erythro-leukemia" which has been applied to the association of true polycythemia with leukemia does not deserve a demarcation as a separate disease entity, since opportunities to observe over prolonged periods have shown that the leukemic element always represents a transition from the polycythemic phase (41). The cases that have been reported of a transition in the reverse direction are of doubtful validity (42). It may require many years to observe the transition from a leucamoid reaction in the blood to the terminal classical clinical and morphological characteristics of a myeloid leukemia (41). As far as we are aware, no instance of a transition to lymphatic leukemia has been reported. It is of course possible for a lymphatic leukemia to be associated with a polycythemia, due for instance to obstruction of the superior vena cava by a mediastinal leukosarcoma, but in such instances, the polycythemia is compensatory and secondary as proven by a lowered oxygen saturation of the blood. In uncomplicated polycythemia vera, the oxygen saturation is normal. Whether all individuals with polycythemia vera would ultimately transform into a myeloid leukemia, provided they did not die from intercurrent disease, or whether an additional factor stimulates this transition, it is of course impossible to say. In view of the lowered resistance to leukemic invasion in experimental animals by x-ray and the extraordinary frequency with which leukemia develops in "leukosarcoma" following similar treatment, it is probable that this factor acts as a stimulus (43, 44).

*The transition of myeloma (plasmocytoma) into plasma cell leukemia.* Although myeloma is usually limited to the bone marrow, extraosseous growth, especially of the lymphatic structures, have been reported and when these represent the original manifestations of the disease, the diagnosis of plasmocytoma is made. It is questionable whether "plasmocytoma" represents a separate entity, as some aver, or not. Jackson (45) and his coworkers do not believe so and regard both myeloma and extramedullary plasmacytoma as different manifestations of a



generalized neoplastic disorder of the lymphatic system. The matter of classification of plasmacytoma and myeloma is confused by the fact that the plasma cell and the myeloma cell resemble each other so closely, and what appear to be typical instances of myeloma, are reported as of the plasma-celled type and reversely. Whether such a distinction is valid is questionable, because both are derived from the same parent cell, the lymphoid type. There are undoubted plasmocytomata that are extraosseous and remain extraosseous. These have been recently reviewed by Hellwig (46). The extramedullary myelomatous invasion of parenchymatous organs, for instance the liver, spleen and kidneys, associated with an unusual invasion of the circulating blood with plasma cells creates a variant that has been termed "plasma cell leukemia." Most of the reported cases of plasma cell leukemia are associated with myeloma of the bone, Bence-Jones proteinuria, and hyperproteinemia, and many are accompanied by plasma or myeloid infiltration of the parenchymatous organs. Piney and Riach (47) divide myeloma into the leukemic and aleukemic types. Rubinstein (48) postulates that myeloma bears the same relation to plasma cell leukemia as lymphosarcoma to lymphatic leukemia. In one of his cases there were 60,000 cells of which 65 per cent were plasma cells. In another there were 23,000 cells with 16 per cent plasma cells and 8 per cent myelocytes. Patek and Castle (49) report a case with 50,000 leucocytes of which 33 per cent were plasma cells. Most of such reports represent counts made in the terminal phases. When counts are made serially from the early to the terminal phases, there is as a rule, a progressive rise both in number and percentage of the young forms. Thus Rubinstein reports a rise in the total white blood cell count from 6,000 to 26,000 and a percentage increase of plasma cells from 0.5 to 38 per cent. However, plasma cells may never appear in the blood at any stage, even when there is a pronounced myeloid invasion of the parenchymatous organs as in the case of Churg and Gordon (50).

*Monocytic leukemia.* The precise status of monocytic leukemia within the rubric of the leukemias is still debated, although its behavior is precisely like that of established forms of leukemia, both clinically and in respect to aleukemic state (51, 52, 53, 54), its association with tumor formation (51, 55, 52, 54), and the hematological mutations (52, 56, 57). One of the difficulties as Forkner (52) says lies in the different interpretation of its origin; whether it comes from the lymphocytes, the primitive mesenchymal cells (58), the endothelium, or the reticuloendothelium. With the supravital and peroxidase stain technique, Sabin, Doan and Forkner (58) proved to their satisfaction that the monocyte is a specific cell. However this has not been substantiated by others (59, 60, 61). It seems to us that it is not a question whether the monocyte is a specific cell of a precise origin, but whether it represents a phase in the maturation of the cells of primordial cytoplasmic reticulum which includes all the above mentioned tissues. It is not the specificity of the cell but the dominance of the type that determines the present day classification of the monocytic leukemias. As a matter of fact other unripe cells other than the monocytes have been frequently noted in the blood, especially cells of the myeloid series (51, 62). Doan (57)



followed a case of myelocytic leukemia for twelve months and at one time there appeared a shower of monocytes in the blood so that they comprised a large per cent of the total white cells in the blood. Mitchell (54) also reports such a change, which he believed followed x-ray therapy. On the other hand, Kracke (59) and Ederle and Esch (56) have noted a number of monocytic leukemias that terminated in a definite myeloid leukemia. The factors that determine the predominance of the monocyte at some phase or the other in the course of the malady is again unknown, and will probably remain so until the cause of leukemia is discovered. In all likelihood, therefore, monocytic leukemia represents a phase of myeloid leukemia.

Monocytic leukemia is often associated with what is termed a "reticulosis." It is difficult to appraise what is meant by this lesion, since the interpretations are so diverse. It is sometimes referred to as a "hyperplasia" and sometimes as a "neoplasia" with potentialities toward the development of reticulum celled sarcoma or lymphosarcoma (63). Some regard reticulosis as originating in the reticulo endothelial system, and therefore the cells that enter the blood stream are "reticuloendothelial" in type. Others regard "reticulosis" as "hemocyto-blastosis" and therefore belongs to the aleukemic or leukemic histioblastoses (12). As a matter of fact, all these various transitions have been reported, with neoplasms and without neoplasms, with leukemia and without leukemia and in various sequences.

It would appear that if cell specificity is ruled out as the criterion in the interpretation of leukemia and a biological approach is made based upon the potentialities for differentiation of the cytoplasmic reticulum of the myeloid and lymphoid tissue, it will bring unity to a much confused subject. In addition one needs as Richter (64) insists, a better understanding of the process termed "hyperplasia" and "neoplasia."

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## Samuel Bookman, Ph.D.

December 1, 1869–October 8, 1946

At the time when Mount Sinai Hospital moved from its former location on Lexington Avenue, and 67th Street to its present site, Dr. Samuel Bookman's services were enlisted first as unofficial advisor in the construction and planning of a new separate Department of Physiological Chemistry and on February 1, 1902, he was appointed Associate in Physiological Chemistry. Ever since, he remained one of the most loyal members of the hospital staff, full of pride and ambition for the Hospital.

Dr. Bookman, born in New York City, the son of Jacob Bookman and Caroline Meyer Bookman had graduated after education at Public School and Dr. Julius Sachs' School, from the Columbia School of Mines in 1891. His graduate work at the University of Berlin, which at that time was a center of chemical learning under Emil Fischer, led in 1895 to the degree of Doctor of Philosophy under Professor Siegmund Gabriel who was not only an excellent organic chemist, but an outstanding teacher. Dr. Bookman's work dealt with the preparation and reactions of  $\beta$ - and  $\gamma$ -ethoxybutylamine (Ber. d. deutsch. chem. Gesellsch., 28:3111, 1895). Dr. Bookman recalled that at one time during these Berlin student days Professor Gabriel introduced in his lecture an impressive old man with a big beard, Johann Ludwig Wilhelm Thudichum; he was both a physician and a chemist who had had to leave Germany about 1848 because of his democratic convictions, and after a few years in Switzerland, had come to London. There he established a chemical laboratory at St. Thomas' Hospital and thus became the first Hospital Chemist. Amongst many other achievements, he laid the foundation for the chemical knowledge of the brain and became the father of lipid chemistry. It was but in the 'nineties that his merits were recognized in Germany and that he received an honorary degree from Berlin University at which occasion Dr. Bookman met him.

Dr. Bookman upon his return to the United States, was soon appointed Associate in Physiological Chemistry in the Pathological Institute of the New York State Hospital. Under the direction of Ira Van Gieson there were assembled in this institute a number of promising young men including the chemist Phoebus A. Levene, the psychologist Boris Sides, Harlow Brooks, then bacteriologist, and Ales Hrdlicka, the anthropologist. The institute was an intellectual and training center from which modern scientific methods emanated into the recently established laboratories of the State Hospitals.

When Dr. Fred S. Mandlebaum, Director of Laboratories of Mount Sinai Hospital, was planning laboratories for the new hospital site, Dr. Bookman, called as advisor, brought with him splendid qualifications to establish the first Chemistry Department in any voluntary hospital in New York City.

During the ensuing years Dr. Bookman went to Europe several times for post-graduate studies and spent some time with Friedrich von Mueller in Munich, and, in 1910, a six-month term back in Berlin, with the renowned biochemist



To the Chemical Laboratory  
Mt. Sinai Hospital

S. Bookman

Emil Abderhalden, then chemist at the Charité. These study trips as well as the scientific intercourse with numerous prominent chemists and men in related fields and, last but not least, an eager group of chemically interested physicians on the staff of the Mount Sinai contributed to the successful conduct of the laboratory: the routine service mirrored Dr. Bookman's personal characteristics, punctuality, and meticulousness, paired with a genial and cheerful spirit of service.

In collaboration with Albert A. Epstein he studied the formation of glycocoll in the body and found it independent of the protein metabolism. The excretion of benzoic acid remained uninfluenced by administration of leucine or alanine. These observations, carried out not only on normal experimental animals, but also after hepatic liver damage had been produced by phosphorus, foreshadow the hippuric acid excretion test for liver function (*J. Biol. Chem.*, 10: 353, 1912; 13: 117, 1913; 17: 455, 1914). A comparison of renal and vesical calculi led to a discussion of their formation under the influence of diet, acidity, infection and other factors (*J. Biol. Chem.*, 29: xxix, 1917). In addition to his own researches, Dr. Bookman inspired and guided his clinical collaborators in the laboratory leaving them a wide scope for their activities.

Fortunate to be able to serve through all these years without remuneration, he arranged for the distribution of private fees amongst his collaborators who, thus, gained greater freedom to pursue their research work in exchange for performing certain analytical tests for the hospital.

Planned during the first world war, the new laboratory building replacing the old laboratory on 101st Street was opened in 1922 on 99th Street, where both routine and research work in the Department of Chemistry were continued on an expanded scale. A list of the associates and assistants of Dr. Bookman and of the problems which they investigated will be found in an article entitled "Twenty-five Years of Physiological Chemistry at the Mount Sinai Hospital" (1902-1927) contributed by himself to the Eli Moschcowitz Memorial Volume (*J. Mt. Sinai Hosp.*, 12: 87, 1945).

When the laboratories were reorganized with a full-time paid staff in 1927, Dr. Bookman was appointed Consulting Chemist to the hospital. While this position left him more time to devote to his family and to his other interests, he did not take his consulting duties lightly. He was a frequent regular visitor to the Chemical Laboratory and his eager interest in the laboratory activities, his sound and experienced advice, and his intercession to obtain much needed improvements were a source of welcome encouragement to the laboratory staff and will remain a cherished memory.

Dr. Bookman's marriage to Olga Blum was blessed with three children: his only son Dr. John J. Bookman who is at the present time rounding out his medical curriculum as resident on the Hospital's staff, had been captured in Corregidor while serving in the U. S. Navy Medical Corps. Dr. Bookman Sr., although under the shadow of his last illness, kept up his courageous spirit and lived to see his son return.



Dr. Bookman's lot in life was a happy one, both in its domestic and its professional aspects; he led a full life and, except for the end, enjoyed a healthy vigorous constitution. Owing to his congenial temper, his ingratiating ways and his straight outlook, we remember him as always at peace with the world, beloved by all who had the privilege to be associated with him. While we mourn his loss, we feel that the Hospital was fortunate to have counted Dr. Bookman for the greater half of his life amongst its staff. We shall keep his memory forever dear.

Harry Sobotka

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT  
SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Infections of the Nasal Accessory Sinuses and Ears in the Aged.* H. ROSENWASSER. Arch. Otolaryng., 41: 182, March, 1945.

Senescent changes in the body as a whole and locally in the nose, nasal accessory sinuses and ear are responsible for altered physiologic function. This explains the oft times unusual manifestations of infections in the aged, so at variance with analogous infections in younger people. These modifications must be clearly understood and appreciated if the clinical picture in the aged is to be evaluated properly. Some general clinical features of accessory sinus disease and otitic infections in the aged have been observed. The obvious disproportion between the minimal clinical signs and symptoms and the extensive destruction found at operation in type III pneumococcus mastoiditis in the aged is worthy of emphasis. In view of the high mortality of the complications of acute infection of the upper respiratory tract in the aged, efforts should be directed toward prevention of involvement of the sinus and middle ear. Because of the consistently high incidence of mastoiditis complicating acute middle ear suppuration in the aged, these patients should have early and adequate chemotherapy. Chemotherapy should also be given in cases of severe acute sinusitis in order to prevent initiation of complicating general diseases, such as coronary thrombosis, bronchopneumonia and bronchial asthma with their attendant high mortality rate. There are many aged patients, who have never learned to accept their advancing years gracefully and philosophically. Their attitude must be borne in mind when they come for treatment; and to obtain the best results, one must treat them with consideration, infinite patience and gentleness.

*Penicillin for Scarlet Fever.* M. I. SALOMON. J. A. M. A., page 684, March, 1945.

A healthy white boy aged 6 years contracted fairly severe scarlet fever with rectal temperatures reaching 104 to 106°F. On the fourth day, pronounced asthenia and severe multiple synovitis appeared. Since the onset he had been given adequate doses of sulfadiazine and small doses of acetylsalicylic acid for the control of the fever and the arthralgias. The parents refused serum. On the fourth day after the appearance of the rash it was decided to suspend all other medication and inject 5000 units of penicillin to every 3 hours. After the second injection the fever began to fall and the temperature became normal on the following day. The most surprising effect was on his joint pains, which seemed to disappear under the influence of the penicillin. It was realized that care must be taken to avoid "post hoc ergo propter hoc" judgment. However, the temperature in scarlet fever does not return to normal by crisis, but by lysis, and in this instance it returned by crisis.

Aside from some traces of albumin, the urine was repeatedly normal. The diagnosis of scarlet fever in this patient was firmly established. As far as is known, penicillin has not hitherto been used in scarlet fever.

*Studies in Developmental Pathology. III. Disintegration in the Nervous System of Normal and Maldeveloped Embryos.* P. GRUENWALD. J. Neuropath. & Exper., Neurol. 4: 178, April, 1945.

The embryonic brain of mammals and birds shows areas of rarefaction and cysts, most commonly in the corpora striata and thalami. In human embryos there is also extensive cyst formation in the cerebellum. All these changes disappear again. Similar formations occur in or near malformed parts of the nervous system in chick embryos, in regions where they do not normally appear. Their further development is unknown. The possible bearing of these observations on the pathology of the nervous system is discussed.

*The Roentgen Features of Eosinophilic Infiltrates in the Lungs.* H. HENNEL AND M. L. STUSSMAN. *Radiology*, 44: 328, April, 1945.

The resemblance of these pulmonary infiltrates to the lesions seen in exudative tuberculosis has frequently led to the erroneous diagnosis of atypical pulmonary tuberculosis. The bizarre distribution of the pulmonary densities is quite characteristic and should suggest the correct diagnosis; the finding of an eosinophilia will confirm it. While the pulmonary infiltrates frequently resolve in a few days, they may last for weeks and months. In some instances analogous exudative reactions may occur in other organs and tissues. The associated clinical features are usually mild and of short duration; they may, however, be of considerable severity and last for weeks and months. There is a definite allergic background in most if not all of these patients. Five representative cases are discussed and illustrated.

*Physiology of Mucus Secretion.* F. HOLLANDER, *J. Nat. Cancer Inst.*, 5: 367, April, 1945.

This is a brief review of previous work from this laboratory on the physicochemical and histological characteristics of gastric mucus secretion obtained from dogs by the use of various chemical stimuli. Statistical analyses of these data are given with preliminary discussion of the possible significance of the results. The characteristics of the mucus which are discussed are: pH, chloride concentration, buffer capacity, and cell content—the latter in particular relation to gastritis.

*The Flying Blood Bank.* A. Kaplan. *Pacific Fleet Medical News*, 1: 14, April, 1945.

An account is given of the U. S. Naval Whole Blood Distribution Center as it served on Guam. Only type "O" blood was used and it was utilized generously because it was simple to administer. In stressing the superiority of whole blood over plasma or serum albumin particular point is made that the red cells in whole blood have as their main mission the transportation of oxygen to various parts of the body. By bringing adequate quantities of oxygen to injured tissues shock can be shortened or prevented. The efficiency and value of the Flying Blood Bank was proven on Guam shortly before the Iwo Jima campaign.

*Gastric Resection for Duodenal Ulcer.* R. LEWISOHN. *Surg., Gynec. & Obst.*, 80: 355, April, 1945.

Gastric resection is at present the most popular method in the surgical treatment of duodenal ulcer. However, occasional attempts are made to put the clock back and to reintroduce gastroenterostomy. The term "partial gastrectomy" should be applied to the operation performed for duodenal ulcer. The difficulty of comparing statistics from different hospitals is discussed. We cannot classify a case as a "healed ulcer," unless the specimen shows evidence of a previous ulceration. The mortality following gastric resection for duodenal ulcer has been reduced in recent years. It is now as low as that of gastroenterostomy.

*Intrasternal Transfusions in Obstetrical Hemorrhage.* M.D. SCHNALL AND R. J. HEFFERNAN. *Am. J. Surg.* 63: 1, April, 1945.

For obstetric patients with severe hemorrhage and collapsed peripheral veins, intrasternal administration of whole blood and plasma may prove life saving. A brief history

of the intramedullary route for giving fluids together with indications, precautions, and descriptions and photographs of the technic are included. An ordinary 15 gauge needle, inserted with the bevel up through the periosteum over the manubrium or the body of the sternum below the angle of Louis, is held at a 30 degree angle with firm, constant pressure. Lack of resistance is noted when the anterior plate of the sternum has been pierced. A 2 cc. syringe with 1 cc. saline is connected to the needle and 0.1 to 0.2 cc. of blood-marrow mixture is aspirated; after 2 cc. of saline has been injected slowly, the gravity infusion apparatus is quickly attached to the needle in the sternum and the rate properly regulated. The needle is firmly fixed in the compact layer of bone and is not easily dislodged. It may remain for several days in place without after effects if strict asepsis has been maintained.

*Myelography by the Use of Pantopaque in the Diagnosis of Herniations of the Intervertebral Discs.* A. B. SOULE, S. W. GROSS AND J. G. IRVING. *Am. J. Roentgenol.*, 53: 319, April, 1945.

The authors report their experience with the use of pantopaque in the diagnosis of herniations of the lumbar and cervical discs. Their study is based on 129 myelographic examinations in which surgical exploration was carried out in 77 patients. The technic for lumbar and cervical myelography is described in detail. In the lumbar region the following abnormalities in the opaque column are described: Block defects, gap defects, veil defects, "hour-glass" defects, lateral pressure defects and root defects. In 11 patients two herniated lumbar discs were found at operation. The correct diagnosis was predicted from the myelogram in every case. The authors prefer pantopaque to other contrast media for the following reasons: 1. It is one-seventeenth as viscous as lipiodol. Therefore it can be introduced and removed with ease. In 86 per cent of their cases the authors were able to remove 95 per cent or more of the pantopaque. 2. It moves up and down the spinal canal more readily and has less tendency to break up into globules. 3. If left in the subarachnoid space it is slowly absorbed. Myelography should precede exploration for a herniated disc since it offers objective evidence as to the presence of a lesion and provides valuable information regarding multiple herniations. The procedure is simple, safe and accompanied by very little discomfort to the patient. In this series, in cases with positive myelograms, the nature of the lesion was predicted in all but 2 of 77 operated upon. On 1 case a herniated lumbar disc was diagnosed whereas at operation an extradural metastatic tumor was found. In the other case a cervical cord tumor was suggested by the myelogram; at operation a herniated disc was found.

*Penicillin Therapy of Sulfonamide-Resistant Gonococcal Infections and Associated Complications in the Male.* A. COHN and B. A. KORNBLITH. *Am. J. Syph. Gonorr. & Ven. Dis.*, 29: 334, May, 1945

One hundred and thirteen selected cases of sulfonamide-resistant gonococcal infections in male patients were treated with penicillin, in an attempt to determine a satisfactory schedule of penicillin therapy for ambulatory patients. Two schedules of penicillin therapy were tested. In both schedules a total dosage of 100,000 Oxford units of penicillin, administered intramuscularly, was found both necessary and sufficient for bacteriologic cure. In the first schedule, treatment was divided over a period of 6 hours; an initial injection of 50,000 Oxford units of penicillin was followed by 2 subsequent injections of 25,000 Oxford units each at 3 hour intervals. Eleven cases thus treated became bacteriologically negative within 4 hours after therapy was begun, and remained negative throughout an average follow-up period of 7 weeks. In the second schedule of treatment 102 patients received a total amount of 100,000 Oxford units of penicillin within a period of 4 hours. The penicillin was dissolved in 9 c.c. of normal saline and injected intramuscularly in 3 c.c. doses at 2 hour intervals. A total of 100 cases in this group responded promptly to the first course of therapy. Cases with complications of gonococcal infection responded promptly in all of

the cases treated. Bacteriologic cures were consistent. Post-gonococcal prostatic involvement was unaffected by further penicillin therapy.

*Symposium on Ulcer Problem; Synthetic Predigested Aliment for Jejunostomy Feeding.* F. Hollander, S. Rosenak and R. Colp. *Surgery*, 17: 754, May, 1945.

The clinical uses of jejunal alimentation are briefly reviewed. Reasons for the current lack of widespread use of this feeding procedure are analyzed, in relation to the physiologic factors concerning the composition of the nutrient material. The formula for a synthetic predigested ALIMENT is presented, together with the method of its preparation. In contrast with previous formulas, emphasis is laid on the incorporation of partially predigested proteins, a marked reduction in the fat content, the use of partially predigested carbohydrates free of hexose sugars, and a liberal supply of essential vitamins and salts—especially excess sodium chloride. Evidence for the efficacy of this nutrient mixture is given, based on its administration to experimental animals and patients with jejunostomy. Preliminary investigation having justified the clinical use of the ALIMENT in preference to other feeding mixtures, it is now being used in this Hospital for a variety of feeding problems as well as for cases with jejunostomy.

*Methyl Alcohol Poisoning. Report of 42 Cases.* A. Kaplan. *U. S. Nav. M. Bull.*, 44: 1107, May, 1945.

Forty-two cases of methyl alcohol poisoning were recognized and treated shortly after the invasion and conquest of one of the islands previously held by the Japanese. The cases are grouped according to symptoms as mild, moderate and severe. The mortality was 32 per cent. Four to eight ounces of the poison was sufficient to cause death or blindness. An individual tolerance was noted in the analysis of the symptoms presented by the patients. On the average, they arrived at the hospital 24 to 36 hours after the drinking bout. Symptoms were first noted 6 to 12 hours after intoxication and in order of appearance they were: blurring vision, splitting headache, epigastric distress, abdominal cramps, nausea and vomiting. In severe cases drowsiness, coma and death followed in quick succession. Six cases showed repeated convulsions of a decerebrate type shortly before death. As is well known, methyl alcohol by oxidation is reduced to formaldehyde which upon further oxidation forms formic acid. Formic acid has a specific affinity for the central nervous system, particularly the optic nerves and respiratory center and vagus nerve. Treatment is symptomatic in combating acidosis. No method to prevent the breakdown of methyl alcohol into its deadly components is known. The prevention of methyl alcohol poisoning is far easier than its recognition or cure.

*Multiple Chestleads in localized Damage of the Heart.* B. Kisch. *Exper. Med. & Surg.*, 3: 154, May, 1945.

The explanation for electrocardiographic changes in coronary occlusion or in other myocardial damage should be based on well founded experimental facts which ought to be performed not only with every experimental caution to eliminate errors but also quantitatively. Experiments of this kind performed by the author and his collaborators have up to now yielded 2 facts of importance: 1. The ECG from the peak of R to the end of T depends predominantly or exclusively on the electro-physiologic behaviour of the surface layer of the heart muscle. This behaviour can be changed by changes of the stimulus conduction or by an abnormal biochemical behaviour of the muscle cells at the heart surface. 2. In case of a recent localized damage of the heart, chest-leads taken from different points of the chest wall (CR<sub>1</sub> and CR<sub>2</sub>) show a different and even mirror-image like configuration of their R-S-T part, depending on the site of the damage.



## THE ARTIFICIAL KIDNEY\*

W. J. KOLFF, M.D.

*Physician to the Engelenbergstichting Municipal Hospital, Kampen, Netherlands*

Although the recent war has increased everyone's knowledge of geography, I am not certain that the town of Kampen is known to you. Kampen is a small and old town situated at the point where the river Yssel empties into the Zuider Zee. Once her ships sailed over the seas of the world, but in 1642 the Yssel silted up. All is over now as far as shipping is concerned, but Kampen is the town where the artificial kidney was built.

First of all I want to thank Dr. Abraham Hyman who enabled me to come to your great country and who so graciously introduced me to this audience. I also want to thank Dr. Snapper for the introduction which he gave me to my colleagues in this country.

Of the several forms of uremia—renal, extrarenal, and mixed—I will limit myself to the purely renal type. As is well known, even a case of purely renal uremia becomes complicated by extrarenal factors within a few days and these extrarenal factors must be treated first. If such treatment does not restore kidney function the retention products must be removed by some other method, so that the patient is tided over the difficult period until the kidneys resume their function.

Abel, Rowntree and Turner in 1912 removed retention products from the blood of living animals by dialysis (1). In their apparatus a cannula is inserted into an artery of the experimental animal. Hirudin is introduced from a burette. The blood flows through a tube, then through collodion tubes and returns through collodion tubes to be led back into a vein. Abel, Rowntree and Turner proved that urea and other retention products could be removed by dialysis and they invented the term artificial kidney. They did pioneer work, but as far as I know, they did not continue their studies.

Haas (2) used a slightly modified method in man and Necheles (3) and William Thalhimer (4) have worked on dogs. With the exception of Thalhimer most investigators encountered the following difficulties:

- 1) The lack of a reliable anticoagulant. This difficulty is non-existent nowadays because of the availability of heparin.
- 2) Difficulties with the dialyzing membranes. Modern cellophane or Visking cellulose tubing solves most of this problem.
- 3) The capacity of the dialyzers used previously was too small.

With heparin and Visking tubing available, the only problem left was the construction of apparatus with sufficient capacity for clinical use. Various models have been built and tried out in the course of our investigations, but I shall show only the type we are using at present.

\* Lecture delivered at the Mount Sinai Hospital, March 21, 1947.

A big drum or cylinder turns so that its undermost segment is constantly immersed in a bath of rinsing fluid (fig. 1). Forty-four to fifty-five yards of Visking cellulose tubing have been wound around this cylinder. The tubing only contains a small quantity of blood and this blood always sinks by gravity to the lowest part of each coil of cellophane. When the drum rotates a short distance, the blood sinks again to the lowest level in each coil of cellophane.



FIG. 1. The artificial kidney. Fifty-four yards of cellophane tubing are wound around a cylinder which rotates in contact with a bath of rinsing fluid.

When the drum rotates constantly the blood constantly sinks to the lowest levels of the cellophane coils. In so doing the blood runs through the Visking cellulose spiral from left to right. The blood is under no additional mechanical pressure; there is just a thin film of blood in the cellulose tubing and it runs by gravity only. The blood enters and leaves the rotating cylinder through the hollow axle.

It is our practice nowadays to do continuous dialysis. The blood comes from the radial artery through a glass cannula, it passes a cellophane window, flows through the hollow axle of the drum into the Visking cellulose tube, leaves the artificial kidney through the other hollow axle, and is pumped back by a rubber

tube pump and passes through an air-bubble catcher into a vein of the patient. The rinsing fluid must be clean but need not be sterile, as cellophane and Visking cellulose are impermeable to bacteria. Through the dialyzing membrane molecules go in and out. Therefore we must add to the rinsing fluid whatever we do not want to come out of the blood. At present we use a standard rinsing fluid for all patients with acute uremia. The mineral composition of this fluid closely resembles the mineral composition of normal blood plasma. It contains NaCl 0.6 per cent,  $\text{NaHCO}_3$  0.2 per cent, KCl 0.04 per cent, and glucose 1.5 per cent. The rinsing fluid does not contain calcium since calcium would be precipitated by the sodium bicarbonate. In the absence of calcium from the rinsing fluid the dialyzable calcium of the blood tends to be removed during dialysis.

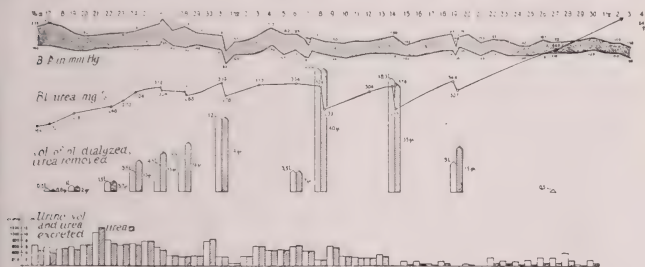


FIG. 2. Graph of the first case in which the artificial kidney was used. The systolic and diastolic blood pressure are shown at the top; the pulse pressure is cross-hatched. Below this is a continuous jagged line which indicates the blood urea; it will be observed that the level drops after each large dialysis. The pairs of erect picket-like bars show respectively the amounts of blood dialyzed and the amounts of urea removed during each application of the artificial kidney. The bar diagram at the bottom of the chart indicates the daily urine volume and the daily excretion of urea in the urine.

For this reason the patient, as long as he is connected with the artificial kidney, is given injections of calcium gluconate. Glucose is added to the rinsing bath in the concentration of 1 per cent in order to prevent hemolysis. If the patient has edema still more glucose is added, in order to attract edema fluid into the rinsing bath.

As far as the clinical results are concerned, uremia is not a good indication for treatment with the "artificial kidney." Nevertheless, the first patient we treated had chronic uremia with contracted kidneys (fig. 2). She was in very bad condition; there was nothing to be lost and perhaps a temporary improvement to be gained. On the first day 0.5 liters of blood were dialyzed. The subsequent 24 hours giving no evidence of untoward reaction, a whole liter was next dialyzed. After a second wait of 24 hours, 1.5 liters were dialyzed. Finally 20 liters were dialyzed and 40 grams of urea removed. Figure 2 shows the decline in the level of blood urea after each major dialysis. Despite these temporary successes, renal function failed to improve and the patient died.

Figure 3 is the record of an exceptionally fat man weighing more than 100 kg. He had acute glomerulonephritis and he entered the hospital with a blood-urea of 700 mg. per cent. This man was given immediate dialysis. One hundred and twenty liters of blood flowed through the artificial kidney and 263 grams of urea were removed. The blood-urea fell from 704 to 192 mg. per cent. Dialysis was administered a second time. The patient died from pulmonary complications. No penicillin was available at that time.

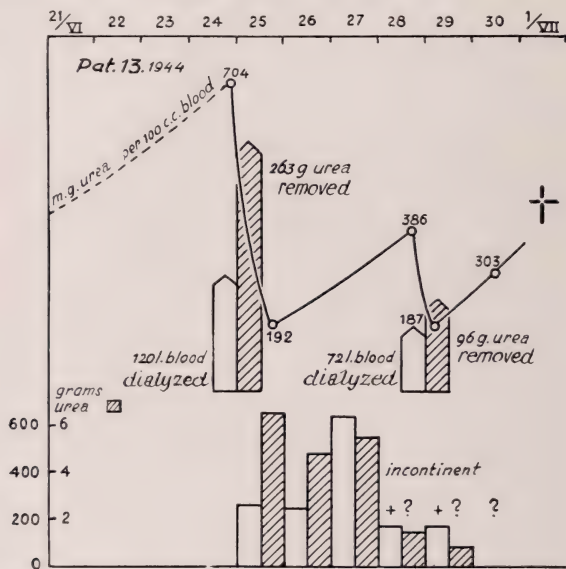


FIG. 3. Acute glomerulonephritis. The blood urea level declined from 704 mg. to 192 mg. after the dialysis of 120 liters of blood, from which 263 gm. of urea was removed. A second dialysis brought the blood urea down from 386 mg. to 187 mg. This patient died of pulmonary complications.

Not only urea is removed by dialysis; other retention products such as creatinine, uric acid, indoxyl, non-protein nitrogen and phosphates are also removed. Special attention should be given to the conduct of the inorganic substances. In one of the early cases the potassium level was reduced to 14.8 mg. per cent. At present potassium is added to the rinsing fluid and the level is reduced to normal values. A high chloride content is reduced and a low chloride content is elevated. A low alkali reserve is raised by dialysis alone. After protracted dialysis the concentration of the minerals in the blood plasma ap-

proaches more and more closely the concentration of the same substances in the bath water.

The clinical result in the first series of fifteen patients was not very promising, there were fourteen deaths. An account of the fourteen deaths has been given elsewhere (in a Dutch monograph (5)) and will not be repeated here. Only one patient survived and he would perhaps have survived without the aid of the "artificial kidney," so that the only thing this observation can prove is that it is possible to be alive after dialysis. The results of the second series of sixteen patients were much better as there were six survivals; of the ten who died nine had chronic renal disease with contracted kidneys. The following examples are taken from the group.

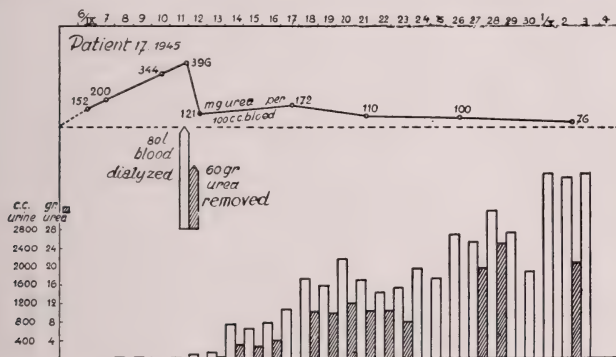


FIG. 4. Cholecystitis and acute glomerulonephritis. Blood urea declined from 396 mg. to 121 mg. per cent. after removal of 60 Gm. of urea by dialysis.

Figure 4 is the graph of a woman 68 years old. She had cholecystitis with pericholecystitis and acute glomerulonephritis with almost complete anuria (a so-called hepato-renal syndrome). When she was admitted to the hospital she was uremic and stuporous. After dialysis the blood-urea fell from 396 to 121 mg. per cent. One day after the dialysis, although the output of urine was almost zero, the patient was quite clear mentally, talked very much, and made plans for her future. It is quite evident that the substances responsible for the clinical picture of uremia, whatever they may be, had passed into the rinsing fluid.

Figure 5 shows the course of a 13-year old girl who was soaked through in a walking contest, developed acute glomerulonephritis and had anuria for a week. At admission she was in very bad condition with pulmonary edema and pneumonia. She was given oxygen and penicillin and was treated with the "artificial kidney." The kidney was filled with her blood in order to reduce





the pulmonary edema and the blood was returned after dialysis. Recovery was uneventful. This case illustrates that edema of the lungs is no contraindication for treatment with the "artificial kidney."

Figure 6 refers to a man of 23 years, who took a teaspoonful of bichloride of mercury. The chart shows how quickly the blood-urea rises owing to the so-

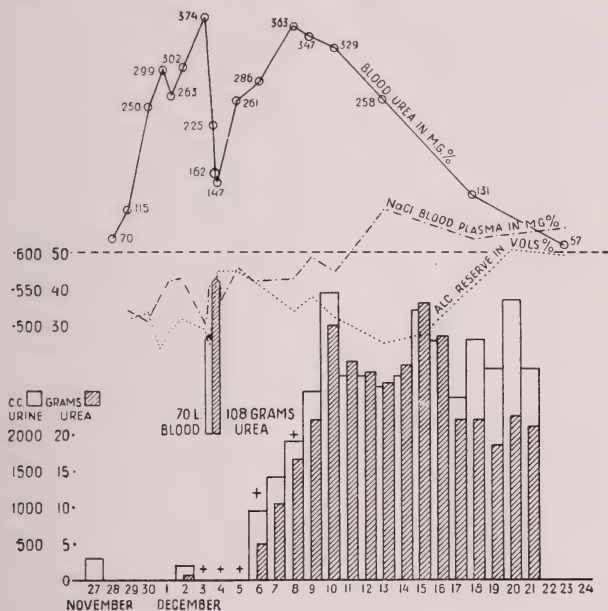


FIG. 6. Mercury poisoning in a man aged 23. By peritoneal lavage 39 Gm. of urea were removed in 24 hours. By means of the artificial kidney 108 Gm. of urea were removed in nine hours.

called toxic breakdown of body protein. The patient was treated with peritoneal lavage and 39 grams of urea were removed in 24 hours. Lavage was discontinued because of swelling and pain in the abdomen, which are not unusual after mercurial intoxication. Then the "artificial kidney" was applied. One hundred and eight grams of urea were removed in nine hours. Diuresis started and the patient is back at work now. Another case of mercury poisoning, treated with BAL (British anti-Lewisite) and with the "artificial kidney," ran very much the same course.

Peritoneal lavage is so well known in this country that the principle need not be discussed. The excellent work of Frank Seligman and Fine (6) who saved a patient from uremia has again stimulated interest in this method. I will only show the method which we used. The first essential is a large amount of rinsing fluid. It has very much the same composition as the rinsing fluid of the "artificial kidney" but  $\text{CaCl}_2$  is added and the rinsing fluid must be sterile.

It is sterilized by boiling in two parts. For this purpose a small and a large tank are used. The small tank is filled with 5 liters of water containing: 130 gr.  $\text{NaCl}$ , 120 gr.  $\text{NaHCO}_3$ , 11 gr.  $\text{HCl}$ . The large tank is filled with 0.23 liters of water containing: 280 gr. glucose, 8 gr.  $\text{CaCl}_2$ , 192 cc.  $\text{HCl}$ , 10 per cent. The small tank is placed inside the large one; the lid is closed and it is sterilized by boiling on a gas range. After cooling the tank is tilted  $90^\circ$  so that the contents of the inner tank flows into the outer through an aperture, and mixture is ensured by shaking. The fluid is kept at  $39^\circ\text{C}$ . and is conveyed through rubber tubes which are introduced into the abdomen through trocars. The peritoneum is used as a dialyzing membrane. The procedure requires constant watching because at any moment an intestinal loop or the omentum may block the outflow.

In one of our patients, who had anuria from bilateral stone disease, there were various contraindications to operation and peritoneal lavage was used twice. Diuresis was started after about 12 days; the stones were subsequently removed.

A little girl 9 years old who was said to have been ill for 3 weeks came in in a very poor condition with a blood-urea of 550 mg. per cent and was treated 4 times with peritoneal lavage. She now felt so well that she asked to be sent to the childrens' ward. She had good appetite and enjoyed herself. Her output of urine, however, remained very small. Later she had convulsions and died. Autopsy revealed the presence of small contracted kidneys.

I feel that dialysis is not an ideal treatment for chronic uremia. We may have something better for the future.

A man with perfectly healthy kidneys was given a uremia diet as devised by Dr. Borst of Amsterdam. This diet consists of 200 grams of butter and 200 grams of sugar a day. The excretion of urea in the urine was reduced to 1 to 3 grams of urea per day. If this man became anuric, he could live for 25 days before his blood-urea would reach a dangerous level.

A comparable result was obtained in a patient with hypertension and mild chronic uremia who was given the rice diet of Kempner. She felt comfortable and her urea output was reduced to 1 to 3 grams per day.

It will be remembered that if the caloric requirement of a patient is taken care of with carbohydrate and fat, the production of urea is reduced and the urea output can be brought as low as 4 grams per day.

We have other plans now. In a patient with severe uremia who knew about his condition and who was vomiting constantly, an intestinal loop one meter long was isolated and the ends were brought through the abdominal wall like an artificial anus. We perfused this isolated intestinal loop. It was possible to remove four grams of urea in 10 hours. This time we took only one meter of ileum—next time we may take two meters.

I hope that I will come back to this country after a year or so and that then I may show you or you may show me a patient who is doing his work in the daytime and who is dialyzing himself through his intestinal loop during the night and in whom both kidneys will have been removed as useless, superfluous, and even dangerous organs.

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## RECENT ADVANCES IN OUR KNOWLEDGE OF VITAMINS<sup>1</sup>

GEORGE R. COWGILL, PH.D.

*Professor of Nutrition, Yale University School of Medicine, New Haven, Conn.*

When first invited to be one of the speakers for your 1946-1947 series of lectures I declined on the grounds that the general subject of the lecture series, namely *Recent Advances in Therapy*, obviously relates to medical practice, and that I am not a clinician but rather a research nutritionist and physiologist and therefore not qualified: I suggested that a clinician be secured for this occasion. My declination was not accepted, my arguments were discounted, and I was assured that if I would accept I might discuss any phase of the general subject of vitamins that seemed appropriate to me. The topic finally selected is that which has been announced, namely, *Recent Advances in Our Knowledge of Vitamins*. In planning my discussion of this subject I have tried to keep in mind the fact that the audience will consist largely of clinicians, and have made my selection of various possible subtopics with the view to consideration of those which should be of greater clinical interest and significance. The general subject of this lecture is of course too broad to be covered completely in the time available. I hope that the topics selected do prove to be of some interest to you.

Some years ago the late Dr. Soma Weiss of the Harvard Medical School wrote me a very interesting letter. In it he discussed some interesting observations he and his colleagues had made in cases of thiamine deficiency. It had been found that such cases usually respond very well to daily doses of from ten to twenty milligrams of thiamine. A few cases had been encountered, however, which failed to respond to such doses. When these exceptional cases were given from fifty to one-hundred milligrams of thiamine daily, they exhibited the desired improvement. How, the letter inquired, are we to explain such remarkable differences in effective therapeutic doses of thiamine? In my reply I stated my inability to offer anything in the way of a dogmatic, scientifically established answer; the most that I could do was to theorize concerning the ways in which individuals can differ with respect to vitamin requirements so far as present knowledge indicates, and to comment on the adequacies or inadequacies of the available criteria by which varying degrees of vitamin deficiency can be judged.

Individuals obviously can differ in many respects and one or more of these differences can, theoretically at least, be responsible for higher vitamin requirements. The ability of the alimentary tract to digest and absorb food materials can be abnormal. Some of the vitamins are known to be made by the bacterial flora; therefore, variations in that flora can conceivably play a role. Such investigations as have already been made in this field clearly indicate that many of the vitamins function in certain processes of intermediary metabolism; if those processes go on to an unusually high degree in the given individual, more of the

<sup>1</sup> Presented as part of a series of lectures entitled *Recent Advances in Therapy*, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on January 22, 1947.



vitamin will be needed. We now know that there are metabolic processes by which some of the vitamins at least are actually destroyed. Let us suppose that these processes are unusually active in our unusual patient. Then an ordinary good diet that would supply sufficient vitamin to most people would not keep this unusual individual in health, with the result that sooner or later he would appear in a doctor's office or a clinic exhibiting signs of vitamin deficiency. Still another consideration that might be mentioned relates to variable excretion of water-soluble vitamins through the kidney and the factors that might influence this. All of these theoretical possibilities were drawn upon in attempting to answer the letter from Dr. Weiss; they are mentioned here because they have an obvious pertinence to our present theme.

In any discussion of the question of vitamin requirement it is pertinent to distinguish between the points of view of the non-clinician and the clinician. The former, represented by students of public health nutrition, home economists, physiologists, research nutritionists and the like, are particularly interested in such questions as these: (a) How much vitamin is required to promote and maintain what might be called a state of *optimal* nutrition? (b) What level of vitamin supply is to be recommended to the housewife, dietitians and others responsible for the feeding of families, inmates of institutions and other groups, and the public at large shall we say, as appropriate for them to aim at providing in the dietaries under their control? If a minimum level of vitamin intake is established by scientific research, i.e., a daily amount that will just keep an individual from developing symptoms of deficiency, how much higher should the level of intake be to provide a reasonable factor of safety against increases in the requirement that might perhaps be due to alimentary upsets, short periods of illness that all of us are heir to, and failure of the dietaries themselves to provide expected amounts because of natural variations in foods, greater losses due to poor handling, overcooking and related factors? You will notice that consideration of such questions as these does not involve clinical matters. Clinicians, on the other hand, view the general problem somewhat differently. One group insists that there is no vitamin-deficiency health problem presented unless there are definite symptoms of some kind. Members of this group argue that such terms as "subnutritive state," "moderate non-clinical deficiency," "sub-clinical deficiency" and the like are really meaningless: since symptoms are not present, there is no clinical entity. This group of clinicians—let us call them the conservative skeptics in this discussion—also argues that too many of the symptoms thus far described in the literature are not specific enough for diagnostic purposes, and therefore any therapy based on them lacks a satisfactory scientific basis. If, because of this, the therapy must be to administer *several* instead of a *single* vitamin, the whole therapy is too much like the old so-called "shot-gun therapy" practiced in the days before the development of our modern science of pharmacology when doctors wrote prescriptions calling for as many as six to ten or more different drugs on the theory that if one of the drugs in the mixture did not help the patient, some of the others would.

Another group of clinicians feels that such an attitude represents an extreme

point of view; that many special signs of deficiency do in fact exist but they are not easily recognized; they are delicate and subtle signs that require special training in order to be noticed, and an astonishingly large number of physicians need special education in these matters. These clinicians might be regarded as the "liberals" in this controversy. As a non-clinical research nutritionist invited to speak on this occasion, I take this opportunity to offer some remarks on this general theme.

It would be well at this point to consider carefully the meanings to be given certain words used in our discussion; to define our terms as accurately as possible. Most physicians, when using the words "sign of vitamin deficiency" probably mean symptoms observable on gross inspection with the naked eye—a good example is the dry eye of xerophthalmia indicative of lack of vitamin A; or they may mean symptoms detected by palpation—calf tenderness suggestive of a lack of thiamine for example. Such signs are quite objective and have the advantage that they can easily be pointed out to colleagues who can then readily confirm them. Where the symptom involves a change in tissues, such as extensive keratinization of epithelial cells, for example, with resultant accumulation of such keratinized cells in certain places carelessly described as "abscesses" by some observers, it is reasonable to believe that we have, not the first sign of a deficiency, but rather a more advanced stage: the deficiency has finally proceeded to the point where a definite and detectible tissue change has occurred. If this view is correct, then we have to deal with the question how to detect the earlier stage. The tissue change may also occur in some internal structure and be completely undetectible in its earlier stages by any relatively simple means. An example of this is seen in the changes taking place in the odontoblastic cell layers of the teeth in scurvy. Some years ago Hojer (1) made these changes in the incisor teeth of the scorbutic guinea pig the basis of a method for assaying vitamin C. Other assays had involved the prevention by test substances of definitely objective signs of vitamin C deficiency such as painful joints due to hemorrhages, for example. In our own work on the vitamin C requirement of the guinea pig (2) it was observed that roughly twice as much vitamin C is required to keep the odontoblastic cells of the incisor teeth of guinea pigs in a perfectly normal state as is needed to prevent the appearance of the outward objective signs of scurvy. Looked at from the point of view of our so-called conservative clinicians, many of our experimental guinea pigs would have had to be regarded as normal and receiving plenty of the vitamin, yet they were in fact subjects of mild or early scurvy.

This situation has its counterpart in the human species. When the Food and Drug Administration established its first daily vitamin minima for use in judging statements on labels, it took as its criterion the amount of vitamin that would just prevent obvious signs of disease. With respect to vitamin C the minimum figure finally selected for man was 25 mg. per day; later this was raised to 30 mg. per day. Recent studies on inmates of one of our state prisons (3), however, show that 25 to 30 mg. of ascorbic acid daily do not suffice to correct gingivitis and maintain the gums in a healthy state over a period of many months. Daily

doses of 25, 50, 75 and 100 mg. of ascorbic acid were tested over long periods. The 25 mg. dose was insufficient in all cases; 50 mg. was not enough; 75 mg. proved to be adequate for all cases except a few men who were also suffering from a chronic infection and whose condition became satisfactory when they received 100 mg. daily. These observations support the figure of 75 mg. daily recommended by the Food and Nutrition Board of the National Research Council (4). Evidently careful examination of the gums can reveal signs of earlier stages of ascorbic acid deficiency than are seen in the classic hemorrhagic symptoms of scurvy, and these more delicate signs have in the past escaped the attention of many clinicians, and I believe they are still not being sufficiently appreciated by a large part of the medical profession.

Recent developments in our knowledge of the factors that contribute to bringing about capillary invasion of the cornea also suggest some comments pertinent to this theme.

In 1937 Day and associates (5) placed rats on diets extremely low in riboflavin and observed the development of cataracts. Two years later, Bessey and Wolbach (6) reported the vascularization of the cornea of the rat in riboflavin deficiency as well as in lack of vitamin A. The attention of clinicians was soon drawn to the importance of examination of the eye in a search for signs of riboflavin deficiency, with the result that capillary invasion of the cornea was reported by Sydenstricker and associates (7) to be a definite sign of ariboflavinosis in man. As often happens in such situations, the original suggestion that capillary invasion of the cornea is a sign of riboflavin deficiency was in my opinion improperly interpreted and extended by many workers in the form of an over-generalization: these clinicians and some non-clinical students of nutrition went so far as to hold that every case of capillary invasion represents riboflavin deficiency. Such a claim was soon challenged in many quarters. Sydenstricker, one of the first clinical workers on this topic and his associates have subjected this matter to extensive laboratory test on the rat, and reported that this capillary invasion also occurs in vitamin A deficiency (8), and amino acid and protein deprivation (9, 10). In their latest communication (11) these investigators report the special importance of a lack of methionine in the development of this interesting vascularization. Totter and Day (12) had reported the appearance of vessels in the cornea of rats deficient in either tryptophane or lysine. Albanese and Buschke (13) extended these observations with respect to tryptophane deficiency. Sydenstricker and associates (9) extended and confirmed these observations in both of these amino acid deficiencies. Their latest report (11) adds methionine deficiency and severe protein deprivation to the list of dietary situations in which this capillary invasion develops in the rat.

Still other causes of corneal vascularization have been reported, namely, zinc deficiency, thallium poisoning and poisoning by tyrosine. From this it is evident that this vascularization cannot be regarded as a specific sign of riboflavin deficiency. Sydenstricker and associates point out that it "is not a universal finding in all deficiencies, though there seem to be causes . . . other than those listed above" (9). This receives support from the observations of Machella and

McDonald (14) made on a series of patients who exhibited the generally accepted clinical picture of riboflavin deficiency including corneal vascularization but none of whom responded with marked improvement upon receiving riboflavin. Lyle, Macrae and Gardiner (15) examined for corneal vascularity the eyes of nearly 4,000 men in the Royal Air Force at 10 stations in Great Britain, and at 12 overseas stations with climates varying from subarctic to tropical. Of the vascularization noted, some was apparently due to lack of riboflavin because it responded to treatment with the vitamin. On the other hand, various experiments suggested that other factors in fruits and vegetables influenced the vascularization more than riboflavin. Treatment with various other pure vitamins did not result in definite improvement whereas supplementing the diet with a good variety of nutritious foodstuffs did. These authors believed that the degree of corneal vascularization in their groups of subjects was a reliable index of the general state of nutrition of the group, but the fact that in some cases there was no response to a superior diet suggested still other non-nutritional causes of vascularization.

Buschke (16) has commented on the ease with which vascularization develops in the cornea of the rat, and therefore one can question the applicability of the findings from rat studies to man. In May, 1945, Sydenstricker (9) had the opportunity to examine the eyes of over two-hundred inhabitants of Leyden, The Netherlands, "who were selected at random from the population. Ten per cent were suffering from famine edema. None of the individuals examined showed corneal vessels."

In their studies of this general problem Sydenstricker and associates have observed certain differences in the pattern of vascularization seen in the animals exhibiting different dietary deficiencies. For example, in riboflavin deficiency the vessels tend to develop fairly long "streamers" from the periphery toward the center, with relatively few connecting or "arching" vessels connecting one streamer with another. In vitamin A deficiency, on the other hand, the connecting vessels are more numerous. When knowledge in this field has crystallized, so to speak, it is not unlikely that such details as these will form a part of what the medical student will be expected to learn and detect in his examination of patients. The interpretation to be placed on what is actually observed will not be simple and easy to arrive at because the signs in question are not sufficiently specific. They will have to be considered along with many others, be given their due weight, but probably will not be decisive. This opinion is based on the situation as it appears in early 1947. A good way to end this particular discussion is to quote from the paper of Lowry and Bessey (73) entitled "The Effects of Light, Trauma, Riboflavin, and Aribioflavinosis on the Production of Corneal Vascularity and on Healing of General Lesions," the last sentence:

"4. The variety of agents and deficiencies which will induce corneal vascularization indicates the need for caution in interpretation of corneal vascularization in man."

Riboflavin should be of interest to clinicians for another reason, namely, the prevention of certain congenital malformations that include the cleft palate.

Over a period of years Dr. Warkany and associates at the University of Cincinnati have been studying the factors responsible for the appearance of interesting abnormalities in the litters produced by rats fed various diets. These congenital defects have been described in some detail. One of the interesting features of the picture is a cleft palate. Various preliminary observations soon led Warkany to conclude that the incidence of this condition was associated with subsistence on faulty diets. Experiments soon showed that the dietary factor of interest was not lack of some mineral nutrient but a deficiency of some member of the vitamin B complex from the maternal diet. Finally, through the use of highly artificial rations containing various B complex factors provided in pure form, Warkany was able to show riboflavin to be the preventive factor (74). It appears that at a certain stage of fetal development there is a critical need for riboflavin that must be met; if it is not met, through sufficient supply to the maternal organism, these particular congenital malformations will develop. The fact that this does not develop in the fetuses of *every* pregnant female may, perhaps, be due to variation in requirement for riboflavin, some animals making better utilization of a borderline supply as compared with others. As a result of these developments I have been informed that at least one prominent clinic in this country has become greatly interested in studying women who have given birth to infants with a cleft palate. Was their diet during that pregnancy poor with respect to content of riboflavin? Do these women give metabolic or other indications that they have an unusually high requirement for this vitamin? These are some of the questions that occur to the thoughtful clinician in this connection. I commend them to your consideration.

It has been suggested by Kruse (17) that Bitot spots represent essentially a thickening of the conjunctiva through proliferation and keratinization of the epithelial cells and therefore can be regarded as signs of vitamin A deficiency. According to this author these spots can be classified as representing various stages of development from earlier ones, that respond to long-continued treatment with large doses of the vitamin, to later stages that do not respond because, according to this view, the tissue changes are irreparable. These ideas have been challenged by several critics largely on two grounds, the first one being that the Bitot spots have been seen too often in what were believed to be "normal" patients—an argument that is not a very strong one in my opinion because many ophthalmologists may undoubtedly have seen them often without really knowing how to interpret them—and secondly, because the spots did not "clear up" or disappear following administration of what were believed to be appropriate therapeutic doses of vitamin A. In rebuttal of this second argument it might be pointed out that Kruse himself emphasized the need for giving really large therapeutic doses over a long period; and unless critics of his views have made the same kind of therapeutic trials one is hardly justified in concluding that such views are completely without foundation. To a nonclinical nutritionist and bystander in this situation it seems evident that we need here some more extensive careful observations in this field with greater attention being paid to the detection and treatment of what Kruse believes to represent the early stages of develop-



ment of the Bitot spots, and the concomitant application of other possible criteria of vitamin A deficiency such as levels in the blood for example. If it should turn out that an appreciable number of such cases followed over a long period did in fact improve when large amounts of the vitamin were provided, this would constitute some confirmation of the Kruse viewpoint. It might, of course, turn out that there are some as yet unappreciated contributory causes, nutritional or nonnutritional in nature, in which case we would have to conclude, as with respect to capillary invasion of the cornea, that the sign is nonspecific but nevertheless useful as an indication that the individual's nutritional state is not, or once was not, as good as it might be.

In similar fashion the specificity or nonspecificity of various other symptoms of vitamin deficiencies that have been reported might be discussed here but time will not permit. Even if we grant that the growing body of information in this field supports the view that these symptoms too often are nonspecific, or not as specific as we should like, I believe there is an important lesson here for clinicians. The very fact that any of these symptoms do appear should cause the thoughtful clinician to direct his attention toward the faulty nutritive state of the patient quite apart from whatever else may be in the picture—cancer, etc.—and do something about improving that nutritive state. It is natural that we should wish to find specific signs of vitamin deficiencies, but let us not worship, so to speak, the word *specific* in this connection. It may seem strange to many of you for me to be making such a point here because in so doing I seem to stress the obvious; however, the failure of so many clinicians even at this late date to devote any real attention to this matter of insuring that the patient receives a diet of unquestioned adequacy is sufficient justification to me.

When one considers the history of the subject it is easy to understand why in our thinking we have regarded the deficiency diseases as distinct and separate clinical entities. The outstanding examples represent essentially outstanding deficiencies of particular dietary factors: thiamine in the case of classical beriberi; nicotinic acid in the case of classical pellagra; vitamin D, calcium and phosphorus and certain interrelationships of them in rickets; etc. More and more, however, we are coming to realize that many of these diseases, especially those involving lack of the B-complex vitamins, are characterized by lack of more than one vitamin and even other non-vitamin dietary factors; in other words they represent multiple rather than single vitamin deficiencies (18). For example, in pellagra there is an outstanding lack of nicotinic acid together with varying degrees of shortage of riboflavin, and thiamine, and perhaps other vitamins, as well as of iron and protein. Such being the case, it seems obvious that a rational treatment should be to provide large therapeutic doses of the vitamins most needed—nicotinic acid in the case of our illustration—together with amounts of other known vitamins that will correct these other deficiencies, frank symptoms of which may not as yet be readily apparent. The amounts of these other vitamins to be supplied should not be so small as to require administration over long periods in order to be effective. In my opinion, based on quantitative studies on animals, they should not be just sufficient to meet a normal day's requirement, but may

quite properly be of the order of three to five or more times this, whereas the large therapeutic dose—of nicotinic acid in the illustrative case we are discussing—should be at least from ten to twenty or more times the daily requirement. Perhaps we should coin the verb *vitaminize* to describe this plan of action because of a rough similarity to the digitalizing of the heart patient. Our object should be to correct all dietary deficiencies as quickly as possible, and then to teach the patient how to keep himself in an optimal nutritive state by appropriate selection of wholesome foods, with or without continued vitamin supplementation thereafter depending upon the presence or absence of complicating circumstances and considerations which make it obviously difficult to solve the patient's problem by mere reliance on a good diet that is satisfactory for most people.

Some recent developments suggest that the amount of vitamins needed for health and to be obtained from food may be greater when certain foods are eaten. Krehl and associates (19, 20, 21), in experiments with rats and dogs, have found that replacement of a large part of the carbohydrate of the ration with corn (a) increases the requirement of the organism for nicotinic acid, and (b) this increased need can be met by either an increased supply of this vitamin or by supplying an appropriate amount of the amino acid tryptophane. These findings help to explain the long appreciated relation of some sort between high incidence of pellagra and the use of corn as a staple cereal in human diets. They are also interesting and significant for other reasons. It has long been known that milk is a valuable food for pellagrins. When nicotinic acid was discovered to be the pellagra-preventive factor, using the term in the sense that Goldberger used it, milk was promptly analyzed for it and found to be low. This left its value for pellagrins unexplained. In the course of Goldberger's work on pellagra he once suggested that the disease might represent a lack of some essential amino acid because his clinical experience had taught him that foods rich in good protein are valuable for the treatment of pellagra. Milk is, of course, an excellent source of the amino acid tryptophane, in contrast to the proteins of corn which are low. In a more recent study Krehl and associates (22) have tested numerous diets for their effects on this nicotinic acid-tryptophane relationship and concluded that all of these situations have as a common basis an imbalance of amino acids, "and, of the specific amino acids so far tested, glycine seems to be one of the amino acids most responsible. This effect is dependent to some extent on the type of carbohydrate used, since glycine exhibits no inhibition (of growth) when dextrin is used in place of sucrose." Woolley postulated that the pellagragenic action of corn may be due to a specific substance, possibly an analogue of nicotinic acid (23), and has reported some success in attempts to demonstrate the presence of such a substance in this cereal (24). Whatever the final detailed explanation of this nicotinic acid-tryptophane relationship may be, it is clear that there are for health certain optimal quantitative values of it and dietary conditions for it, and such optimal relationships can easily be missed on high corn diets unless special attention is paid to securing proper supplementation of the diet with a good source of protein. One is led to wonder what other relationships of this sort exist. Evidently we have here a fertile field for extensive cultivation.

Pyridoxine (vitamin B<sub>6</sub>) is now known to be involved in the metabolism of amino acids through discovery of its role as a co-factor for amino acid decarboxylases (25). As part of a study of tryptophane-nicotinic acid relationships Rosen, Huff and Perlzweig (26) in 1946 reported that the administration of tryptophane to rats leads to prompt excretion via the kidneys of nicotinic acid and the metabolite N<sup>1</sup>-methylnicotinamide. Because of the known relation of pyridoxine to the metabolism of amino acids these authors have now investigated the effect of pyridoxine deficiency in rats upon the synthesis of nicotinic acid. In the course of four weeks of vitamin B<sub>6</sub> deficiency the urinary excretion of N<sup>1</sup>-methylnicotinamide in response to oral doses of *dl*-tryptophane was progressively decreased. This defect was not entirely remedied by restoring adequate amounts of pyridoxine to the diet. Kynurenine, kynurenic acid and xanthurenic acid, metabolites of possible interest here, were also studied. The authors concluded that none of them can replace tryptophane as a precursor of nicotinic acid in the rat. I call your attention here to the point that a deficiency of pyridoxine definitely affected the metabolic processes involving tryptophane-nicotinic acid relationships. Mention has already been made of the fact that vitamin deficiencies in man are usually multiple rather than single in nature. If lack of pyridoxine can affect the metabolic picture of tryptophane-nicotinic acid relationship as seen in analyses of the urine for various metabolites in rats fed carefully controlled diets of known composition, how difficult it must be for clinicians to interpret their data when making similar studies on patients who have subsisted on various faulty diets for long periods; and whose exact vitamin deficiencies cannot be stated very precisely. In view of this I would argue that in the long run we are more likely to make rapid progress in our understanding of these clinical deficiencies through the performance of precise biochemical studies on animals fed carefully controlled diets of known composition than we are through attempting similar studies on patients. From such animal studies we should be able to obtain clues as to what dietary factors, metabolic substances and conditions are significant and therefore to be watched closely in the studies made on patients.

Pyridoxine is interesting to consider for another reason, namely an apparent relation of it to fat. It is very difficult to produce in experimental animals the typical acrodermia-like picture of pyridoxine deficiency—the original picture study of which led to the final discovery of vitamin B<sub>6</sub>—when the animals are fed diets relatively high in fat. Evidence is also at hand suggesting that to a certain extent the essential unsaturated fatty acid, linoleic acid, has anti-acrodermic potency. Quackenbush and collaborators (27) have studied the relation to rat dermatitis of pyridoxine, pantothenic acid and linoleic acid. Under the conditions of their experiments linoleic acid was the primary indispensable factor for the cure of the acrodermia-like disease in rats.

"When present in sufficient amounts it cured the acrodermia without the addition of pyridoxine; when present in subcurative amounts its effectiveness was increased by the addition of pyridoxine."

These authors stated further that

"essential fatty acids hold a dominant position in acrodermia since when fed alone they can prevent or cure it. This is evidenced in a number of ways: Pyridoxine can delay the

appearance of the symptoms and in some cases produce temporary healing. It can increase the efficiency of linolate to diminish the amount required to cure acrodynia. Pyridoxine together with pantothenic acid can alleviate or prevent the development of severe dermal lesions on a diet virtually free from essential fatty acids."

Attempts by Quackenbush and Steenbock (28) through analysis of body fat in rat acrodynia to reveal the mechanism by which pyridoxine, pantothenic acid and linoleic acid protect against acrodynia were not successful.

These developments are interesting because they help to explain why the acrodynia-like disease which was produced in rats by faulty diets many years ago, and the study of which led to the discovery of pyridoxine, did not prove to be the exact counterpart in the rat of the acrodynia seen in children; the latter has not responded to treatment with pyridoxine and therefore cannot be regarded as simple pyridoxine deficiency. Judging from the work of Quackenbush and associates, this acrodynia in rats is another example of a complicated deficiency. In this case we have an apparent interrelationship of some sort between essential fatty acid and one or two of the members of the vitamin B complex.

What significance might this have for clinicians? At the present time the Council on Pharmacy and Chemistry and the Council on Foods and Nutrition of the American Medical Association and the Food and Drug Administration of the federal government do not permit therapeutic claims to be made for pyridoxine because of lack of acceptable scientific evidence duly recorded in the literature. Clinicians interested in producing such evidence are naturally looking for patients upon whom to make their clinical trials of pyridoxine therapy. Perhaps it would help if they were to continue making tests with cases of acrodynia but this time working on the hypothesis that other factors besides pyridoxine are involved. Also, the search might, perhaps, be extended to cover various conditions in which the body's handling of fat is impaired, or low-fat diets must be fed, or conditions which have had some attention hitherto as representing possible shortage of essential fatty acid; or to approach the matter from the protein standpoint, that is to say, make the tests on conditions where high protein diets must be fed. These are possibilities that the thoughtful clinician might explore in this connection.

Examples of interrelationships of vitamins to other dietary factors are not limited to those already mentioned. In the case of the fat-soluble vitamins there are the interesting observations of Hickman and associates (29, 30, 31) showing that vitamin E, in its capacity as an antioxidant, can protect carotene, vitamin A and palmityl ascorbic acid from oxidation in the intestinal tract. In the third paper of their series these authors offer the suggestion "that the tocopherols which actively control the oxidative changes in the intestines may be found useful clinically in conditions of intestinal derangement." Their latest contribution (32) extends this line of observation to include study of the interrelation of alpha-tocopherol and essential fatty acids. The tocopherol was shown to spare essential fatty acid and to extend the effectiveness of suboptimal quantities of linolate in preventing and curing the symptoms of lack of essential fatty acid in the rat.

The fat-soluble vitamins are of clinical interest here in relation to another

theme, namely, the abuse of mineral oil as a laxative, and more particularly the use of mineral oil in salad dressings and other foods as a substitute for the more expensive digestible vegetable oils. The Council on Foods and Nutrition of the American Medical Association (33) has published a special report on this topic which is worthy of the attention of all practising physicians. From the animal experiments of many investigators it is evident that mineral oil can dissolve in the intestine and keep from absorption into the body amounts of carotene, vitamin A, vitamin D and vitamin K great enough to produce definite deficiencies of these respective dietary factors. Confirmation of these findings on animals has now been obtained on human patients (34, 35). A most recent development of interest in this connection is the preparation of salad oils in which mineral oil has entirely or almost entirely replaced food oils, and the promotion of such products to the general public for use in reducing diets. Such a practice is definitely against the public interest. Reducing diets are of course designed to be low in caloric content. Next to butter, certain natural food fats and fish oils as valuable sources of vitamin A and carotene are the green leaves of salad dishes, which at the same time are high in water content and therefore desirable for use in reducing diets. These mineral oil salad dressings, however, are definitely promoted for use with such foods, and can dissolve out and keep from absorption the fat soluble vitamins present therein. Unless such products are used strictly under the supervision of a physician who takes the precaution of seeing that large amounts of these vitamins are obtained from some other source—cod liver oil, vitamin K parenterally, etc.—their use is definitely deleterious. Physicians who still feel that mineral oil is the laxative of choice for their patients should give special attention to this problem.

The fat-soluble vitamins are not the only ones whose absorption from the intestinal tract may be interfered with by the presence in the tract of special substances. Various adsorbents are ingested for one therapeutic reason or another. Chronic diarrhea can obviously contribute to the development of what Jolliffe (36) has called "conditioned malnutrition." Kaolin has long been used for the control of diarrhea when the causative agent is capable of being adsorbed. Good examples of this are seen in cases of food poisoning or infection by certain toxic organisms. In addition to adsorbing toxic substances, various adsorbents can also adsorb enzymes and specific nutrients, certain vitamins for example. Melnick, and collaborators (37) have made a study of the influence of the concomitant ingestion of fuller's earth and of kaolin on the availability of thiamine to man. It appears that

"whereas the availability of thiamine was markedly reduced by the fuller's earth, no interference occurred when kaolin was taken along with the thiamine. Indeed, the latter adsorbent appeared to protect the vitamin during its passage through the gastrointestinal tract so that the greater-than-theoretical value for available thiamine was obtained."

The final sentence in their paper deserves quoting here:

"The present experiments cast doubt upon the wisdom of taking continuous large doses of adsorbing agents, unless precautions are taken to insure sufficient vitamin intake."



It is pertinent to make some reference here to the experimentally established fact that the availability to human subjects of thiamine from live yeast is very poor. Several workers have contributed to our knowledge of this subject, notably Parsons and co-workers (38) and Hochberg, Melnick and Oser (39). I cannot do better than to quote here from the summary of the paper by Hochberg and associates:

"Despite the facts that (a) most of the thiamine in the live yeast employed in the present human availability study was present in the free form, (b) the yeast was practically ineffective in phosphorylating the vitamin, and (c) there was almost a 100 per cent overage of thiamine in the sample—all of which should favor the presence of available thiamine at least to the extent of the content of thiamine claimed for the product—only 17 per cent of the total thiamine present was physiologically available, or 33 per cent of the claimed potency. The low availability for the thiamine could not be attributed to a slower rate of adsorption of the vitamin from live yeast."

One of the important developments related to vitamins is the perfection of methods for studying the nutritive requirements of bacteria and other microorganisms. It is now possible to prepare artificial media containing all but one of the substances needed for certain bacteria to grow; when that missing factor is supplied in graded amounts, corresponding rates of growth result. From work in this field has already come a long list of microbioassays for numerous water-soluble B vitamins and even a large number of the amino acids. These methods are sufficiently delicate to permit the determination of extremely small amounts of test substance. Detailed discussion of this particular topic by specialists in the field could very well cover many lectures. I shall limit my remarks concerning it to a few general observations.

For some years now nutritionists have appreciated that the bacterial flora can play important roles in determining whether an animal will be adequately nourished on a given experimental diet. The so-called "egg-white disease" was produced in rats long before the discovery of the vitamin biotin which was first known as one of the bios factors needed for the growth of yeast and shown to be identical with "Coenzyme R" a substance needed for the respiration of certain bacteria. It is now known that biotin is produced by the intestinal flora, and that raw eggwhite contains a substance *avidin* which forms a firm union with biotin keeping it from being absorbed and used by the host organism. "Egg white disease" of rats is now known to be essentially a biotin deficiency. It has also been demonstrated that the ingestion of certain sulfa drugs can, under particular dietary conditions, so affect the bacterial flora as to bring about a deficiency not only of biotin but of some other B complex vitamins as well. Phenomena of this sort should be of great interest to clinicians, because they indicate that when these sulfa drugs are administered in order to combat intestinal infections, the physician must take pains to see that such therapy does not produce vitamin deficiencies at the same time.

Wright and associates (40) have studied in some detail the effects of feeding succinylsulfathiazole to rats receiving various purified diets. The investigation dealt with such points as growth of the rat, the bacterial flora of the feces, and

fecal elimination and liver storage of folic acid, biotin and pantothenic acid. When fed the sulfa drug in high protein diets as contrasted with high carbohydrate and high fat rations the rats continued to gain in weight for longer periods; some of the signs of nutritional deficiencies which became apparent in the latter groups did not appear in the rats fed the high protein diets. The inclusion of the drug in all the diets was accompanied by a marked reduction in the hepatic stores of folic acid and biotin; the stores of folic acid were, however, somewhat higher in the rats fed the high protein diets. The authors make the interesting statement that "of the determinations made, the hepatic stores of pantothenic acid showed the best correlation with the condition of the animals." Another paper (41) by these same authors reports on the effect of varying the carbohydrate component of the ration. The inclusion of sulfathiazole in highly purified diets, irrespective of the source of carbohydrate used, was effective in producing combined folic acid and biotin deficiency. The intestinal synthesis of folic acid, and consequently the amount available to the animals, was depressed directly by administration of the sulfa drug.

This type of deficiency apparently can also be produced by the administration of large doses of the antibiotic agent streptomycin which, like the relatively insoluble sulfonamides, is poorly absorbed from the intestinal tract. Emerson and Smith (42) fed rats a high level of streptomycin in conjunction with a purified diet, and the animals developed signs similar to those observed in experimental biotin deficiency. Furthermore, the animals responded to biotin therapy. Microbiological analyses indicated that there had been a decreased synthesis of biotin. Deficiency signs ascribable to a lack of folic acid or vitamin K were not observed. The authors conclude their paper with the following statement of general therapeutic interest: "These findings would seem to indicate that for the temporary sterilization of the gastro-intestinal tract streptomycin might be more effective than succinylsulfathiazole." Evidently clinicians cannot use certain of these antibiotic agents indiscriminately and carelessly without running the risk of developing vitamin deficiencies. This field certainly deserves further exploration.

Sulfanilamide has been called the first antivitamin to be discovered. The term *antivitamin* now applies to a long list of compounds each of which competes biologically with, or antagonizes the action of a particular natural vitamin. Thus pyriethamine, a thiamine analogue containing a pyridine ring instead of the thiazol ring, was synthesized by Woolley and White (43) and shown by feeding experiments with mice to antagonize thiamine with the result that the animals developed symptoms of thiamine deficiency that could be prevented or cured by sufficient amounts of thiamine. This substance also showed appreciable antibacterial action against *Staphylococcus aureus* and slight action against *Escherichia coli* (44); however, bactericidal concentrations of the drug could not be attained in the blood of mice with doses below the toxic level for the mice. More recently another thiamine inhibitor was reported (45), namely the 2-n-butylpyrimidine homologue of thiamine, the tests having been made with weanling rats. In similar fashion one might cite here antivitamins that act against

riboflavin (galactoflavin) (46), pantothenic acid (pantoyltaurine, thiopantothenic acid, pantothenyl alcohol, phenyl-pantothenone) (47, 48, 49, 50), biotin (avidin, desthiobiotin, biotin sulfone, etc.) (51), ascorbic acid (glucoascorbic acid) (52), para-aminobenzoic acid (various sulfa drugs), nicotinic acid (pyridinesulfonic acid) (53), and vitamin K (4-hydroxycoumarin, 2,3-dichloro-1,4-naphthoquinone (54, 55). In addition Woolley (56) has reported tests on mice that might be interpreted as meaning that alpha-tocopherol quinone is an antivitamin against vitamin E. This substance can be viewed as a structural analogue of both vitamin E and vitamin K. The anti-vitamin K substances are probably of the greatest immediate interest to physicians because of the clinical importance of hypoprothrombinemia.

Folic acid is the latest of the vitamins to be identified chemically and synthesized in the laboratory. The exact structural formula was announced on May 29, 1946 (57). "Pteroylglutamic acid" has been suggested as an appropriate name for the vitamin based on the chemical structure. With the pure substance made available, more satisfactory clinical trials and a variety of biochemical researches of great significance became possible.

"Vitamin M," the antianemia factor needed by the monkey has been identified as folic acid (58). Clinical tests reported by numerous investigators (59, 60, 61, 62, 63, 64, 65) all testify to the importance of folic acid in the treatment of the macrocytic anemia that occurs in certain cases of pregnancy, pellagra, sprue, and pernicious anemia. It appears that folic acid is valuable for the treatment of those anemias that are characterized by a megaloblastic bone marrow both in adults and in infancy and childhood. According to Zuelzer (62) who has reported on trials with infants and children, it has proven to be "ineffective in any of the other anemias of infancy and childhood investigated thus far."

The remarkable effect of folic acid on the steatorrhea of sprue has led Darby, Kaser and Jones (66) to study its influence on the absorption of vitamin A and carotene by patients with sprue. The results were clearly positive.

"In all four cases studied the initial low carotene levels have gradually increased to essentially normal values following therapy with 5 to 15 mg. daily of pteroylglutamic acid. In one patient a relapse of the disease was accompanied by the lowering of the serum carotene and a second remission induced by therapy with pteroylglutamic acid was accompanied by a rise in serum carotene level. During a complete remission induced by pteroylglutamic acid the vitamin A absorption curve assumed a normal character."

The authors state further that

"these results, together with the previous reports of alterations in the glucose tolerance curves of patients with sprue treated with pteroylglutamic acid, indicate that this new vitamin plays an important role in maintaining normal absorption from the gastrointestinal tract."

While discussing the subject of anemia it is pertinent to point out that pyridoxine (vitamin B<sub>6</sub>) has been shown to be important for the prevention and cure of a severe microcytic hypochromic anemia developing in dogs fed certain artificial diets, and previously treated unsuccessfully with iron therapy (67, 68). A relatively low level of supply of pyridoxine is needed for growth compared

with the high level required to protect pyridoxine-deficient dogs against the development of this hypochromic microcytic anemia (69). Wintrobe and associates (70) have reported similar observations in pigs fed a pyridoxine deficient diet, and a rapid regeneration of blood accomplished and restoration of cells to normal size after pyridoxine had been administered. Also ducklings placed on an artificial diet lacking pyridoxine show failure of growth and the development of a severe microcytic anemia which responds promptly to the administration of this vitamin (71). The blood picture here is characterized by a drop in hemoglobin, red cell count and hematocrit. The response to pyridoxine is exceedingly prompt; an immediate resumption of growth is also noted. These striking observations made on an anemia produced in so many different species certainly suggest interesting clinical possibilities as worthy of study.

In conclusion let me stress again that in planning this discussion I purposely tried to select, in relation to the general theme, topics that would seem to be of special clinical interest. No doubt I have omitted some important topics which certain members of this audience would have selected. The recent (December 14, 1946) announcement (72) that para-aminobenzoic acid is especially valuable in the treatment of spotted fever could be made the basis of a discussion of this important nutritive factor for bacteria, and the interesting question whether it should properly be classified as a member of the vitamin B complex. This could logically lead to consideration of the question of relation of nutritive state, more particularly vitamin supply, to resistance to infectious agents, a question that will doubtless be with us for some time to come and which needs considerably more exploration before we shall be in a position to deal with it in any dogmatic fashion. In view of the time available these and many other attractive themes will have to be passed over here. Even so, considering just those that have been discussed, I think you will agree with me that there have indeed been many interesting recent advances in our knowledge of vitamins significant for clinical medicine.

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## FENESTRATION FOR OTOSCLEROSIS\*

SAMUEL ROSEN, M.D.

Deafness in otosclerosis does not occur unless and until the pathological lesion invades the oval window and renders the stapes fixed and immobile. Therefore, it is necessary to differentiate the pathologic lesion in otosclerosis when accompanied by stapedia fixation from that without stapedia fixation. The former is designated as *clinical otosclerosis*, which at present, is probably too inclusive a term, as there may be other pathological conditions which render the stapes immobile. In any event the patient would be deafened for the same reason, namely, the immobility of the stapes impeding air conduction of sound to the cochlea. The pathological lesion of otosclerosis may occasionally involve the round window, nevertheless, it may be said, at least for the present, that the fenestration operation is performed for the condition of progressive deafness due to stapedia fixation.

This stapedia fixation is tested on the operating table by trying to move it with the point of a myringotomy knife placed upon the capitulum of the stapes. Probing the stapes forcibly in this manner in all directions gives the feeling as though the stapes had been fixed in hardened cement. It does not give or move at all. One who has thus probed many stapes in the cadaver and has felt the easy mobility finds a most extraordinary difference in the feel of the rigid and immobile stapes. One might use the analogy of the palpation of a loose tooth which can be moved in its socket as compared to a healthy tooth tightly fixed in its socket.

The fenestration operation, for improving hearing in the above type of cases, rests on the simple principle of creating a new window in the bony labyrinth to replace the malfunctioning oval window with its fixed stapes. This new window is made in the vestibule of the labyrinth close to the oval window exposing the endolymphatic membrane and is covered with the tympano-meatal flap. Sound-waves impinging on the tympanic membrane and skin flap are thus transmitted to the membranous labyrinth and cochlea (figs. 1 and 2).

The operation consists of the following steps: an endaural incision; incomplete exenteration of the mastoid bone; skeletonization of the three semicircular canals; removal of the posterior bony canal wall; removal of the incus and head and part of the neck of the malleus; a specially devised plastic tympano-meatal flap; creation of a fenestra in the dome of the vestibule which is finally covered by the plastic flap.

Although the many variations manifested in clinical otosclerosis render the diagnosis, at times, difficult a patient with the following signs and symptoms would be an ideal candidate for the fenestration operation: a history of familial deafness; bilateral progressive deafness for air-borne sounds of the conductive type; hearing for bone conducted sounds is prolonged over and above hearing by air-conduction in the frequencies in which the hearing by air-conduction is

\* From the Otological Service, Mount Sinai Hospital, New York.

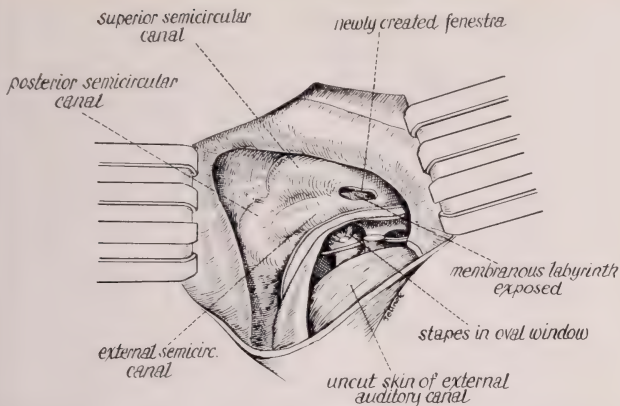


FIG. 1. Drawing illustrating facial nerve between stapes below and newly created fenestra above, and the membranous labyrinth exposed in the vestibule. This fenestra is covered by a new plastic intact continuous flap of the drum membrane and skin of the external auditory canal (extremely thin) shown in Figure 2. (after Lempert)

*thin cutaneous membrane of external auditory canal*

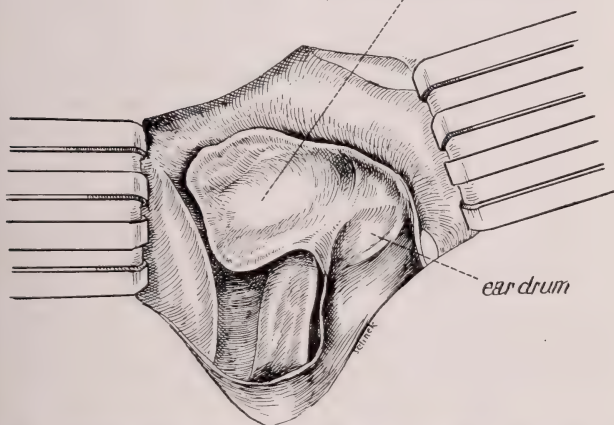


FIG. 2. Drawing illustrating the tympanomeatal flap covering the newly created fenestra. The integrity of this plastic flap is necessary for a successful result. (after Lempert)

impaired (fig. 3a and b). The drum must be intact and the eustachian tube patent. Patients are uncomfortably aware of their tinnitus and report that

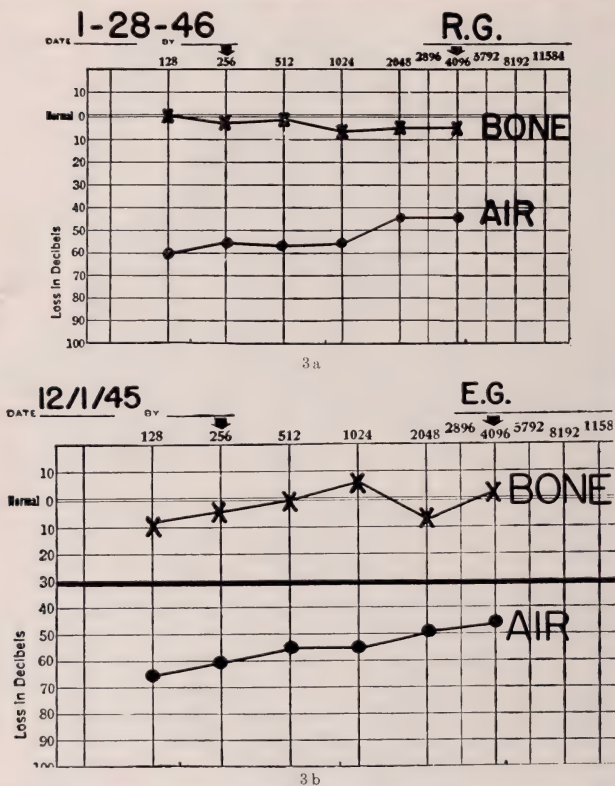


FIG. 3 a. Audiogram, considered ideal for fenestration. Bone conduction excellent, indicating good cochlear nerve integrity, in a patient, aged 38, with progressive deafness for past ten years.

b. Audiogram, considered ideal for fenestration. Bone conduction excellent, indicating good cochlear nerve integrity, in a patient, aged 30, with progressive deafness since 19 years of age; an older sister extremely deaf.

they hear conversation better in noisy places. The ear canals are wide; the tympanic membrane thin and the inner tympanic wall appears pink.

All forms of non-surgical therapy for improving the hearing in otosclerosis have failed. Hearing aids were practically the only recourse. Patients who



do well with a hearing aid should not be urged to submit to this operation. However, since the otosclerotic lesion ultimately involves the cochlea, progressive deafness results, then, not only from involvement of the sound conduction mechanism (fixed stapes) but also from nerve involvement (cochlea). When the latter condition becomes quite apparent, the effectiveness of the hearing aid diminishes proportionately. Unfortunately, when such nerve deafness supervenes (indicated by reduced bone conduction) the patient is no longer a suitable case for fenestration (fig. 4). The success of the operation necessarily depends upon a well functioning cochlea. Since the course of otosclerotic deafness is, as a rule, progressive and can be accurately predicted, the patient should be made aware of what is likely to happen as time passes, so that he may effectively prepare to meet coming events, or consider fenestration operation.

The fenestration operation, skillfully performed, offers restitution of practical, unaided hearing for ordinary every day needs in a large percentage of cases.

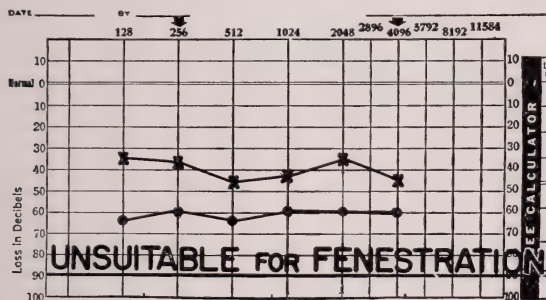
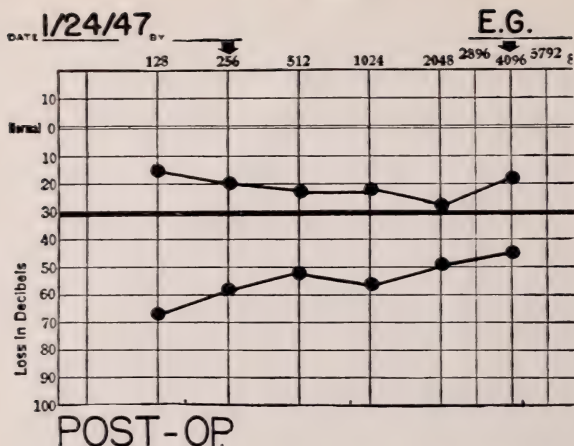
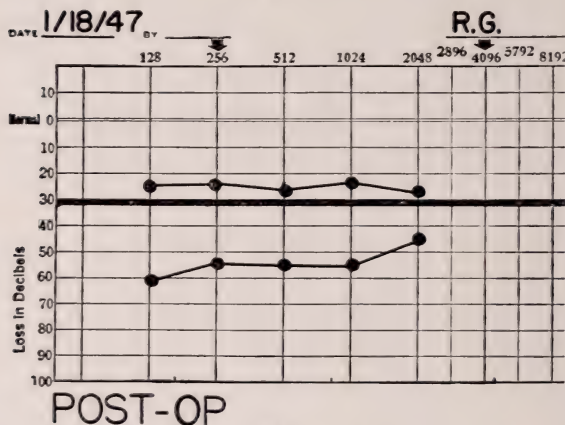


FIG. 4. Audiogram revealing nerve deafness. Bone conduction poor. Case unsuitable for fenestration.

The figures are now based upon statistics numbering many thousands of operations. The more experienced surgeons at present report the chances for restoration of practical hearing at about 60 per cent. Six out of every ten suitable cases skillfully operated upon are likely to achieve practical, serviceable lasting hearing (fig. 5a and b). The remaining four may still retain some improvement over their preoperative level or in some cases the hearing may gradually diminish to the preoperative level. Occasionally, the hearing is worse after fenestration; in about five per cent of the patients, hearing is never improved. Should the operation fail to improve the hearing an aid may still be used, as it may have been previously. The considerable number of deafened patients whose hearing has been restored to the practical level, and has been maintained there for a period from one to seven years, gives ample evidence to prove that the principle of fenestrating the labyrinth is physiologically valid. The operation takes about one and one half hours to do and is performed under local anaesthesia and sedation.



5a



5b

FIG. 5 a. Post-operative audiogram. This patient was fenestrated in January 1946. Her pre-operative audiogram is shown in Figure 3b. She is well above the 30 decibel level of practical, serviceable, unaided hearing. She can hear the thud of a small straight pin dropped on her living-room rug. The curve below the 30 decibel line is the pre-operative air conduction hearing.

b. Post-operative audiogram. This patient was fenestrated in January 1946. Pre-operative audiogram is shown in Figure 3a. Patient now hears well above 30 decibels and has practical, serviceable unaided hearing for all social and economic intercourse. The curve below the 30 decibel line is the pre-operative air conduction hearing.

The fenestration operation as devised by Lempert requires perfection in the performance of every detail. This operation, as every new surgical technique, is undergoing continuous change and improvement, and every change in technique must be carefully tested. Every revision or change in technique is deliberately instituted not to "prove" that a hypothesis is correct *but* to "test" the hypothesis.

There are two recognized causes for failure in the fenestration operation. The first is the osteogenetic closure of the newly created fenestra. The second is a postoperative labyrinthitis due to unavoidable traumatic inflammation of the flap covering and the extension of this inflammation to the membranous labyrinth. When these two factors are avoided the fenestration operation should restore hearing in almost all the suitable cases of clinical otosclerosis.

In any given case one cannot accurately predict the result of fenestration so it is best to choose for operation the ear which has the poorer hearing. The patient must be acquainted with all the details of his problem, the chances for success or failure, and accordingly should be prepared to take the risks inherent in the operation. The patient should also be informed that the hearing improvement may be retained for six months, or more, only to gradually decline to the preoperative level. As a rule, however, when the practical hearing level (30 decibel level) has been maintained for a year after fenestration it is likely to remain so. If the practical hearing level has been maintained for two years then in all likelihood that may be considered as a permanent result.

The operation, itself, constitutes no danger to life. Occasionally, a transitory facial paresis due to perineuritis may occur which recovers quickly. Post-operative infection sometimes occurs in the mastoid cavity but usually is followed by spontaneous recovery.

The two patients whose audiograms are presented here were operated upon by me over a year ago. Both patients have practical, serviceable, unaided hearing for all their needs. The tinnitus has completely disappeared in both patients.

## PARAHYPOPHYSEAL EMBRYONAL RESIDUES\*

### A BRIEF NOTE

PAULO F. L. BECKER, M.D.\*\*

The embryonal rests theory of Cohnheim, amplified by Ribbert and Wilms (1) and strengthened by subsequent observations, assigns to embryonal residues a significant place among the causative factors in the genesis of neoplasms. The following three cases serve well to support this concept.

*Case 1* (Adm. #548867) exhibits the coexistence of a craniopharyngeoma, multiple neurofibroma and a pial meningioma.

*History.* A woman, aged 41 years, was operated upon, elsewhere, for a right acoustic neuroma one year before admission to The Mount Sinai Hospital. There followed at first some improvement but the residual ataxia and slurring speech became progressively worse.

A neurological examination revealed signs of involvement of the motor and sensory branches of the trigeminal nerve, the facial nerve and the vestibular and cochlear branches of the acoustic nerve on the right side. Signs of cerebellar dysfunction were present and were more marked on the right side. X-ray studies of the skull showed "some deepening of the sella turcica, atrophy of the posterior clinoids, slight blunting of the dorsum sellae, and exaggerated convolutional markings in the calvarium." The cerebrospinal fluid findings were negative except for an elevation of the total protein.

*Course.* While under observation the patient passed through two episodes of fainting. During the second episode her pupils became fixed in dilatation.

A suboccipital craniotomy was performed. A right acoustic neuroma was found and partially removed. The patient's condition remained grave after the operation. Aspiration of the wound yielded dark, hemorrhagic fluid and it seemed likely that the patient was bleeding from the tumor bed. She died seven days after operation without regaining consciousness.

*Post mortem findings.* Gross examination disclosed several intracranial tumors (fig. 1). A large and hard mass was found in the ventral portion of the dorsal longitudinal fissure and extended into the medial sulcus. Two other large tumor masses were situated on either side of the brain stem in the pontofacial angle. The spinal cord displayed many small neurofibromata on the spinal roots.

*Histological observations.* The large mass occupying the ventral portion of the dorsal longitudinal fissure was found to be a meningioma. The two acoustic tumors were neurofibromas.

The pituitary on microscopic study disclosed another significant embryonal rest. Between the pars nerva and pars anterior there were several cranio-oral duct remnants (figs. 2a and b).

*Comment.* Although Erdheim (2) found such remnants in about 77 per cent of the normal hypophysis, the finding of the cranio-oral remnants in this case is of particular interest in view of their coexistence with other neoplastic lesions in the same brain. The importance of these cranio-oral duct remnants are now

\* From the Neuropathological Laboratory of The Mount Sinai Hospital, presented before the Section of Neurology and Psychiatry of The New York Academy of Medicine on December 10, 1946.

\*\* Fellow of the Public Health Department of the State of Rio Grande do Sul, Brazil, and International Institute of Education.

accepted as the essential source of so-called craniopharyngeomas, hypophyseal duct neoplasms.

It is significant that craniopharyngeomas and certainly their primordial structures may exist unrecognized for some time because of a lack of symptoms. However, sooner or later, frank neurologic signs appear depending on the extension and topography of the developing suprasellar or intrasellar tumors.



FIG. 1. Ventral surface of brain, showing three distinct tumors indicated by arrows.

Globus (3) has called attention to the fact that tumors of this derivation often differ in their morphology. The different features are due to the dominance of one or another component in the embryonal rest. Thus, it has been suggested (4) that solid craniopharyngeomas (adamantinomas) arise from the remnants of the antero-superior portions of the craniopharyngeal duct, while cystic tumors take origin from residuals of the postero-inferior portion of the duct.

In the case reported here the coexistence of three types of tumors are in accord with the view that they probably have arisen from residues of several different primordia.



*Case 2 (Adm. #550299) exhibits the occurrence of an hemangioma in an adenocarcinoma of the hypophysis.*

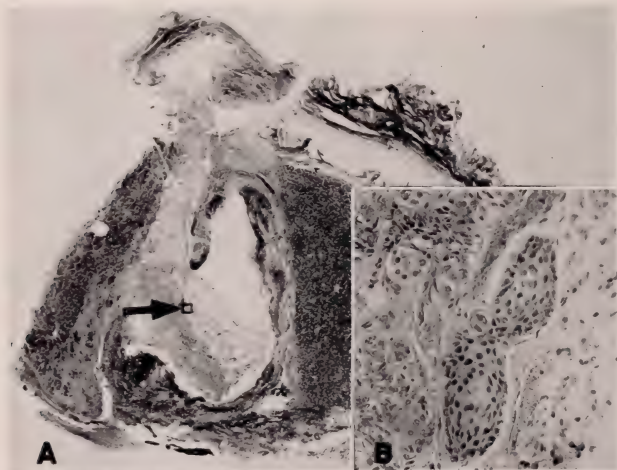


FIG. 2 a. Low magnification of the hypophysis containing a portion of the infundibulum.  
b. Cranio-oral duct remnants, under high magnification, contained in the blocked out area in fig. 2a.

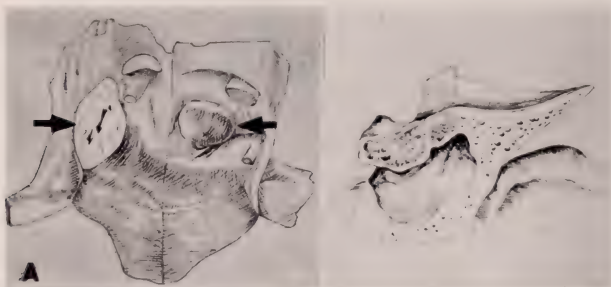


FIG. 3 a. Drawing showing the dorsum sellae and two masses protruding through the diaphragma sellae.  
b. Sagittal section of the same region, showing the enlarged and neoplastic hypophysis.

*History.* The patient, a woman aged 58 years, was brought to The Mount Sinai Hospital in a state of coma. Two weeks earlier she became bedridden, lethargic and finally comatose. She was said to have manifested signs of Parkinsonism during the three years preceding the acute illness.

*Examination* revealed an extremely cachectic, markedly dehydrated and deeply comatose woman. The pupils reacted sluggishly to light. The corneal reflexes were sluggish. There were moist rales at both bases. Her blood pressure was 60 systolic and 40 diastolic. The pulse was 140 with an irregular rhythm.

*Course.* She was thought to have a bilateral broncho-pneumonia. Her temperature ranged between 105° and 106.4°F. She died twenty-four hours after admission, without regaining consciousness.

*Post mortem findings.* Gross examination showed a tumor occupying an enlarged and partially destroyed sella turcica. A protrusion appeared through the diaphragm, grossly continuous with the underlying intrasellar tumor (figs. 3a and b).

*Histological observations.* Serial sections of the tumor were prepared and studied. It was found that the main tumor mass was that of a pituitary adenocarcinoma. Within the center of this neoplasm there was a well circumscribed dense mass of convoluted blood vessels with thick hyalinized and occasionally calcified walls (fig. 4).

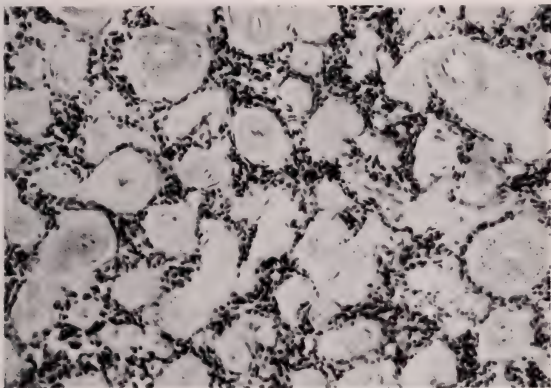


FIG. 4. An hemangiomatous formation within the adenocarcinomatous pituitary. Portions of hypophyseal tissue envelope the individual vascular formations, which are thick-walled and hyalinized. Several contain fine granular calcified material.

*Comment.* Obviously, the adenocarcinoma of the pituitary enclosed a hemangioma. That hemangiomas of the hypophysis are rare was pointed out by Kraus (5). Heuser (6) and Gottlieb (7) have described such a tumor in case of dystrophia adiposogenitalis. A recent review of the intracranial vascular tumors and malformations is given by Noran (8), and there it is pointed out that some observers believe that such vascular neoplasms are mere congenital anomalies.

Of interest is the fact that the hemangiomatous vessels in the case herein reported have undergone a form of mummification for they no longer were physiologically active.

The coexistence of an adenocarcinoma and hemangioma is in line with the view already expressed favoring their origin from an embryonal rest.

*Case 3 (Adm. #544153) exhibits a microscopic meningioma.*

*History.* A man, aged 52 years, was admitted for operative relief of glaucoma. An iridencleisis was performed on both eyes. One week following admission he was found on the floor, unconscious and incontinent of urine and stool. Vomiting was also noted. This episode recurred soon after, accompanied by generalized spasm of his extremities. Despite all emergency measures, the patient died.

*Post mortem findings.* Gross examination of the brain revealed some atheromatous plaques over the basilar artery and mild cortical atrophy.

*Histological observations.* Several islands of pia-arachnoidal residues with the structural appearance of a meningioma were found within the dura surrounding the hypophysis (fig. 5).

*Comment.* The importance of the arachnoidal remnants as the source of meningiomas was already pointed out by Mallory (9). However, recently in the light of the phylogeny of the meninges the fact was stressed that primordial residues antedating the formation of the meninges are the source of the several types of meningeal tumors. The phylogenetic concept was found to be very

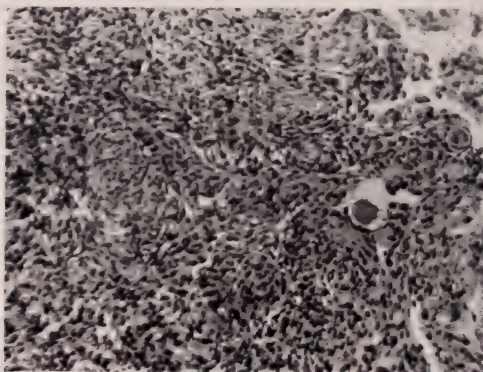


FIG. 5. A fragment of a meningiomatous rest in the parahypophyseal region

useful in adopting a logical classification for the meningiomas (10). In the case reported, the significant feature is the presence of such remnants in the parahypophyseal region explaining the not uncommon occurrence of suprasellar meningiomas.

#### SUMMARY

Several cases are reported in which embryonal residues of varying character were found within or in the proximity of the pituitary body.

Their significance and relationship to the neoplastic formations are briefly discussed.

I wish to express my sincere thanks to Dr. J. H. Globus for his valuable assistance in the preparation of this paper.

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# VENOUS THROMBOSIS AND PERIPHERAL PULMONARY EMBOLIZATION.\*

## PART I

HAROLD NEUHOF M.D.

### CHAPTER I

#### THE DIAGNOSIS OF VENOUS THROMBOSIS IN THE LOWER EXTREMITIES

##### INTRODUCTION

An analysis of the problem of massive fatal embolism of the main stem of the pulmonary artery, based on a study of 88 certified cases constitutes Part II of this monograph. Questions of etiology and prophylaxis are discussed there, with considerable reference to the literature. Part I, appearing a considerable time after Part II, deals with the problem of venous thrombosis and peripheral (sublethal) pulmonary embolization. As originally written there was also considerable reference to the literature, which now is virtually eliminated. The reason for presenting this subject on the basis of personal observations and experiences with little reference to the work of others is to be found in the changing views concerning the management of venous thrombosis. Views on treatment expressed as recently as a year or two ago are often radically altered, sometimes by the same authors. The subject is still in a state of flux and it was therefore thought that the observations and views reached from a study of patients at the Mount Sinai Hospital during the past several years would be of sufficient interest for detailed presentation.

During this interval of time there has gradually developed a much broader interest in the subject as its profound clinical implications have been appreciated. Thus surgeons have come to realize that pulmonary embolism arising from venous thrombosis as a problem in therapy has not been solved by conservative management, that is, the *laissez faire* attitude. Today they have swung to the extreme of very early ambulation of their patients, which undoubtedly reduces the extent of advanced venous thrombosis in the legs but does not solve the problem. Internists are becoming fully aware of the gravity of venous thrombosis in adult patients for whom more or less prolonged bed stay is imperative and not elective. Thus a considerable proportion of patients kept in bed because of coronary thrombosis die of pulmonary embolism and not of the cardiac ailment.<sup>1</sup> By way of contrast one may counter the foregoing with the story of pulmonary embolization, fatal or otherwise, in ambulant individuals who have not been in bed for any medical or surgical illness. Reference to this aspect of the subject will be made and it is mentioned here only to illustrate one of the many

\* This is the first of a series of chapters dealing with this subject which comprises part I of the forthcoming monograph on Venous Thrombosis and Pulmonary Embolism. Part II. has already appeared in earlier numbers of this Journal.

<sup>1</sup> In one report 37 per cent of 100 cases had thrombo-embolic complications which were the cause of death in 12.



facets of the subject. Obviously the subject is one of first importance in adult hospital practice and it is equally obvious that worthwhile progress towards a solution can best be arrived at by the study and efforts of a team composed of those interested and desiring to work on the various aspects of the subject. The limitations of the presentation to be made are in keeping with the fact that there was no team and that the studies which have been made were so largely individual. It would therefore be inappropriate to attempt to cover all aspects of the twin subjects of venous thrombosis and peripheral (sublethal) pulmonary embolization. The presentation will be limited to a survey of observations which have been made, experiences encountered, and operations performed, during the course of study of about 175 patients suffering from venous thrombosis with or without pulmonary embolization. The preponderance of these patients were observed and treated at Mount Sinai Hospital; other cases are added only because of special features of interest.

The subject will be taken up under several captions: 1. The diagnosis of venous thrombosis, including the role of venography. 2. The present status of prophylaxis against and non-operative treatment of venous thrombosis with some reference to administration of concentrated heparin. 3. Atypical clinical forms of venous thrombosis. 4. Some aspects of the diagnosis of pulmonary embolization. 5. The operative treatment of venous thrombosis. 6. The operative treatment of venous thrombosis in the presence of pulmonary embolization, with special reference to management of femoroiliac thrombosis.

#### I. THE DIAGNOSIS OF VENOUS THROMBOSIS INCLUDING THE RÔLE OF VENOGRAPHY<sup>2</sup>

It is safe to say that the incidence of venous thrombosis in the legs in both in-bed patients and in ambulant adults is great and out of proportion to the possibilities of a diagnosis of the lesion. Details of the incidence are to be found in Part II. Mention may be made here to the known incidence of venous thrombosis in Barker's series, which is one per cent of all adult post-operative cases. Of his total of 1,665 cases, 135 were fatal. In the Mount Sinai Hospital series, detailed in Part II, there were 88 proven cases (autopsy) of fatal pulmonary embolism in a period of 10 years. Perhaps the most significant statistics are those of Pilcher who reported that one out of every 20 patients who had clinically recognizable thrombosis died later of pulmonary embolism. In only a third of his 44 fatal cases was venous thrombosis in the legs clinically recognizable. The third point was that 8 per cent of his patients with sublethal episodes of pulmonary embolization died subsequently of massive pulmonary embolism. These statistics virtually state the problem and comprise a demand for improvement of diagnostic measures to say nothing of therapy.

The inherent difficulty in the clinical diagnosis of venous thrombosis becomes evident upon a brief consideration of the nature of the thrombus. This is discussed in some detail in Part II but the essential features should be stated

<sup>2</sup> Capt. Ernest Sarason collaborated in the work reported in this section.

here as they bear on the question of diagnosis. The characteristics of the thrombus from which a pulmonary embolus is usually derived were stated many years ago by Welch. He contrasted the red thrombus which is soft, composed largely of red blood cells (actually all the elements of the blood), and is loosely attached to the wall of the vein, with the white firm thrombus which is composed of platelets, fibrin and leucocytes and is adherent to the vein wall. The red thrombus (bland thrombosis, venous thrombosis) unassociated with inflammation in the wall of the vein is regarded as the usual source of pulmonary emboli, in contrast with the white thrombus which is firmly adherent to the inflamed wall of the vein (thrombophlebitis). However, emphasis should be placed on the danger in the assumption that pulmonary embolization will not occur when there is clinical evidence of thrombophlebitis. This will be discussed later in some detail. Furthermore, on the basis of operative findings it can be said that the bland type of venous thrombosis may be superimposed on obvious thrombophlebitis, and in such cases may be responsible for pulmonary embolization, either peripheral or massive and fatal.

The entire development of what may be termed the progressive present day approach to the problem of venous thrombosis and pulmonary embolism rests on the relatively recent conclusive demonstration that the veins of the legs are the outstandingly common source of pulmonary emboli (excluding the right auricle in heart disease, or other still rarer sites). The most clinching evidence in support of this theory was offered by Neuman in 1938. He studied the veins of the lower extremities by serial section in 165 unselected consecutive autopsies of patients who died of a variety of diseases. Venous thrombosis was found in 100 cases. Neuman observed that venous thrombosis began in the plantar veins. Involvement of the femoral vein was always the result of propagation of thrombosis from the deep veins of the leg. Of equal significance was the existence of infarction (peripheral pulmonary embolization) in 34 per cent and massive fatal pulmonary embolism in 12 per cent in his series.

Interest in and proof of the existence of venous thrombosis as related to pulmonary embolism appeared to be of little clinical interest until demonstrable proof of the presence of venous thrombosis in the living was set forth. Perhaps this was to be expected because of the difficulty attending accurate diagnosis of venous thrombosis by the usual clinical methods. It was for this reason that the development of venography marked the decisive step in the advancement of our knowledge of thromboembolic disease. The roentgenologic visualization of the superficial and deep venous systems of the lower extremities was first carried out by Dos Santos (1938). Employing a radio-opaque mixture injected into the small saphenous vein at the ankle, he demonstrated that visualization of only the superficial system was evidence of thrombosis of the deep system. Venography as the graphic method in the study of thromboembolic disease was placed on a firm basis by Bauer (1940). He set forth the normal pattern of the deep venous system, its variation as the result of recent or old thrombosis, the unsuspected great extent of thrombi in some cases (upward propagation into the femoral vein), and the frequency with which thrombosis is encountered. One

of his most significant contributions was the roentgenographic demonstration of the free upper portion of the propagated thrombus in the femoral or iliac vein, the attachment to the intima being at an inferior level. Despite certain limitations and difficulties in the interpretations of venograms to which reference will be made, Bauer's classical work provided the essential basis for an understanding of the problem of venous thrombosis and supplied the needed stimulus for active therapy.

The foregoing remarks on the nature of the thrombus together with Bauer's revealing venograms of the frequently unsuspected extent of thrombosis explain the fact that reports in the literature usually make reference to the frequent paucity or absence of clinical evidence of thrombosis in many cases, in contrast to the obvious signs of inflammation characteristic of thrombophlebitis. In our own series clinical evidence was lacking in about one fourth of the cases, although the evidence of thrombosis was slight in a substantial proportion of the remaining three fourths. In some early instances the diagnosis of venous thrombosis was solely inferential, being based on positive venographic evidence encountered in patients suffering from pulmonary embolism. As the role of venography became more and more limited and as more and more attention was given to the possibility of the existence of venous thrombosis the diagnosis was made more and more often on the basis of clinical criteria. An incidence of silent venous thrombosis is conceded but the flat statement can be made that objective signs of the lesion are more frequently encountered as they are more carefully sought for.

A presentation of personal observations may begin by stating that pain in the calf, not infrequently mild and transient, was common. At times it was the sole evidence of venous thrombosis. In several instances rapid extension of pain from the calf into the thigh occurred. While the presence of pain in the thigh or groin has served as good evidence of the propagation of thrombosis from the calf to the femoral and iliac veins (as judged from operative and venographic findings), there also has been clear evidence that upward extension of thrombosis even into the vena cava can and does occur silently. Indeed, signs and symptoms of thrombosis in the femoral region are scarcely to be anticipated if the thrombus is free and unattached to the vein wall in that region. The speed of extension which apparently occurs at times should be noted for it is of considerable importance. An illustrative case is a patient convalescing from a gynecological operation who first complained of calf pain on the fifth post-operative day and of pain in the thigh on the following day. At operation there was a soft thrombus which had extended upwards into the external iliac vein. Propagation of thrombosis from the calf to the iliac vein apparently took place within twenty-four hours.

Objective signs of venous thrombosis may often be as scanty as subjective evidence, yet can often be discovered if carefully searched for, as already mentioned. Homan's sign (calf pain on dorsi-flexion of the foot, the leg being extended) is useful when present but unfortunately is not to be found in more than one third of the cases. Deep calf tenderness is described by some as a positive sign. Alone, however, it is a subjective sign and as such is not of decisive

value. A sign which I regard to be valuable (and which apparently is not mentioned in the literature) is infiltration to be felt on palpation of the deep calf musculature. With the patient's heels resting on the bed, the knees flexed and the calf muscles relaxed, palpation reveals thickening and infiltration deep to the gastrocnemius. The area of infiltration, of greater or lesser extent, is vertically disposed. It usually is tender, although tenderness varies with different patients. The area of infiltration, which corresponds to the general region of the deep veins of the calf, may coexist with subjective signs of venous thrombosis or may be present alone. It is of interest to note that characteristic infiltration of the calf was present in all cases in which Homan's sign was positive, but was also present in a number of cases in which no other objective evidence of venous thrombosis existed.

Increase in the circumference of the calf which is the seat of venous thrombosis ranging from slight to obvious, has been noted in the great preponderance of the cases which have been studied. When slight, it can be identified only by comparison (measurement) of the two calves and is of course of no value if thrombosis exists in both calves. A useful method, if many adult bed patients are being studied for the possibility of the development of venous thrombosis, is to record the calf measurements at the beginning of bed illness by strips of paper (as suggested by Coleman B. Rabin) which can be attached to the chart. These strips would be used from time to time to check on increase in circumference.

Varying degrees of thickening or infiltration along the course of the femoral vein were noted in a number of cases in which in fact femorofemoral thrombosis was usually found at operation. It is of interest to note however that the degree of firmness of the thrombus was by no means always in keeping with the extent of thickening which was felt. In several instances in which the femoral vein was palpable and appeared thickened, operation revealed a soft non-adherent thrombus. Leaving aside consideration of the popular but false sense of security against embolism in the presence of thrombophlebitis, it is to be emphasized that venous thrombosis and not thrombophlebitis may in fact be the pathological state which is encountered at operation. Thus the diagnosis and consequent conservative (non-operative) treatment of thrombophlebitis on the basis of fever, pain, tenderness, and thickening along the course of the femoral vein may be both incorrect and dangerous. A case may be cited in which a patient convalescent from an operation for hernia developed some pain in the calf and fever, soon followed by femoral pain in the anterior upper thigh and continuing fever. On the basis of fever, tenderness, leucocytosis, and a palpable femoral vein, the justifiable diagnosis of thrombophlebitis was made. However, at a time when the local manifestations were subsiding (a few days after they had first been noted) there was the sudden access of an episode of pulmonary embolization soon followed by death from blockade of the main stem of the pulmonary artery.

In summary it can be said that the more frequently venous thrombosis is sought for the more frequently can the diagnosis be made on clinical grounds. The signs usually are scanty. The diagnosis cannot be made solely on sub

ective evidence. The classical Homan's sign may be regarded as pathognomonic when present (one third of the cases). Two objective signs of value and frequently present are infiltration of the calf and increase in circumference of the calf.

The rôle of venography in the diagnosis of venous thrombosis can now be discussed. As Bauer's work became generally known, a number of years ago, a wave of enthusiasm concerning the value of venography in the diagnosis of venous thrombosis in the deep veins of the calf was widespread. At the present time one may say that the wave has receded to such an extent that the method has fallen into rather general disuse. A justification for the limited yet precise and useful indications for the method will be set forth on the basis of personal observations.

A recapitulation of the method of venography as described by Bauer is required because of variations of the method as described by others. With the patient in the supine position the small saphenous vein posterior to the lateral malleolus is exposed and cannulated under local anesthesia. Twenty cc. of iodrast compound solution are injected slowly over a period of 60 seconds. At the end of that period appropriate films are taken to include the calf and the knee joint. Ten and 15 seconds later another roentgenogram to include the region of the hip joint is taken (the method is described in greater detail in Part II).

The partial or complete non-visualization of the deep veins of the calf, usually accompanied by the demonstration of an increased superficial venous system, was regarded by Bauer as indubitable evidence of deep venous thrombosis. Like others at that time we believed complete reliance could be based on the venographic findings if good technique was employed. Venography was employed by us in many cases of pulmonary embolism in which venous thrombosis in the legs was suspected and operation was based on the roentgenographic evidence of obstruction rather than on scant physical signs pointing to venous thrombosis (or on an assumption of venous thrombosis in the absence of signs).

At a time when doubt arose in the minds of some observers as to the complete reliability of venography as a method to prove the existence of venous thrombosis a case came under our observation which established in our opinion the lack of complete reliability of venography. The case is of importance insofar as it proves by actual dissection what had been suspected by others but not proven. The patient, under treatment for severe rheumatic heart disease, suffered an episode of pulmonary embolism. In the absence of signs of venous thrombosis bilateral venograms were done according to Bauer's technique. They revealed a typical pattern of bilateral incomplete visualization of the deep tibial veins and some increase in the superficial venous system (fig. 4 to be compared with the normal venogram as seen in figs. 1, 2, 3). A bilateral ligation of the femoral veins was performed. The patient succumbed to another episode of pulmonary embolism and heart failure. At autopsy a thorough examination of the veins of both lower extremities failed to reveal thrombi in any of the veins, large or small. The pulmonary emboli were derived from the heart. After this observation the conclusion appeared warranted that technical aspects,



with or without the added factor of spasm of veins, rendered doubtful the interpretation by venography of venous blockade in the deep veins of the calf. Thus the method could be regarded as of decisive diagnostic value only if a normal venous pattern had been revealed and thus the absence of venous thrombosis was established.

It eventually became clear that the diagnosis of venous thrombosis which had extended into the femoral veins or beyond was one of great clinical importance. Thrombi derived from the main venous trunks, because of their size, represented the most dangerous potential or actual sources of pulmonary embolism. It was found that the Bauer technique did not offer adequate visualization of the femoral or iliac veins and there were cases in which the clinical diagnosis of femoroiliac thrombosis could not be made. For these cases Marcy Sussman, radiologist to the Mount Sinai Hospital, suggested a technique which has yielded uniformly good results. With the cannula in place, after 20 cc. of diodrast solution have been injected slowly and the films of the calf veins have been taken, an additional 20 cc. are injected rapidly (10 to 15 seconds). Roentgenograms are then taken of the thigh and hip. There is obtained a precise visualization of the femoral and iliac veins and, at times, of the lower part of the vena cava. Varying degrees of obstruction by thrombi influence the pattern which is obtained. In every case in which the method was used the variation in the pattern demonstrated in the venogram was established at operation. The method can therefore be regarded as dependable. These statements are supported by the following cases in most of which the technique, which may be properly termed the Sussman-Bauer technique, was employed for the diagnosis of femoroiliac thrombosis. The cases are described in some detail in the section dealing with operative treatment but are referred to here in connection with diagnosis. They supply the data for this first report on the roentgenographic visualization of venous thrombosis of the main venous trunks of the lower extremities by the Sussman-Bauer technique. Only the first case, with a normal femoroiliac venogram, is described in some detail.

*Case 1.* Adm. #504209. Female, 72 years old, suffered pain in the left chest and shoulder, several hemoptyses, and fever, for a week before admission. There was a past history of two "heart attacks" necessitating prolonged bed rest. The significant features of the examination were a systolic-diastolic murmur at the aortic area and the physical signs and roentgen evidence of a pneumonic consolidation in the region of the right middle lobe. Under hospital observation there was another episode of pulmonary embolization—thoracic pain, hemoptysis. Suggestive bilateral calf tenderness appeared to exist but there was no other evidence of venous thrombosis. The patient's condition was not good enough for any operative treatment other than an imperative one. If operation were indicated it was to be limited to one femoral vein if possible. Accordingly a venogram was carried out on one leg, and when found to be normal, was carried out on the other (fig. 3). On the basis of normal venograms, with special reference to the femoroiliac veins it was assumed that the emboli were derived from another source—heart. In any event the normal venograms of the femoroiliac veins established the absence of a propagating thrombosis in those veins and thus the extreme unlikelihood of the lower extremities as the source of large emboli from which the patient apparently suffered. Accordingly operation was not performed. The patient recovered.



FIG. 1



FIG. 2



FIG. 3

FIG. 1. Normal venogram, postero-anterior view  
 2. Normal venogram, lateral view  
 3. Normal femoroiliac venogram



FIG. 4

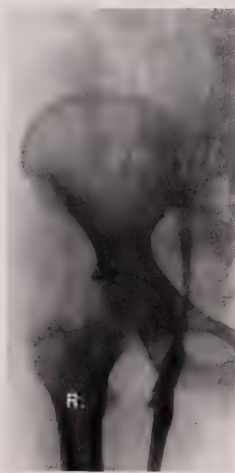


FIG. 5

FIG. 4. a. Incomplete block of deep tibial veins of right leg. Venogram of left leg was almost identical.

5. Termination of profunda immediately below its junction with the superficial femoral vein.

*Case 2.* (Adm. #495572). Male, 42 years old, convalescent from lobectomy for bronchiectasis performed three weeks before. Episode of hemoptysis and pain in the left leg. Because of the question of the relationship of the attack of pulmonary embolism to the operative procedure (film of the chest was uninformative) a venogram was done. It revealed a blockade of the femoral vein extending upwards to its middle third. The femoral vein was ligated. There were no further episodes of pulmonary embolization.

*Case 3.* (Adm. #498887). Female, 52 years old, developed thoracic pain without discomfort in either leg six days after a urethroplasty. There was tenderness of the left calf and lower thigh without other signs of venous thrombosis. The venogram demonstrated a

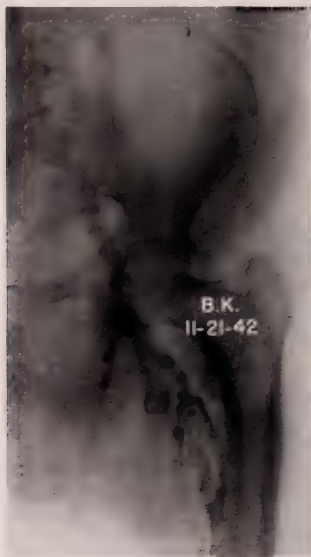


FIG. 6



FIG. 7

FIG. 6. a. Block of superficial femoral vein below its junction with the profunda. Note the cup-shaped termination apparently corresponding with that of the thrombus.

7. Block of the superficial and profunda femoral veins just below their junction.

block in the veins of the calf and thigh, the latter being limited to tributaries of the superficial femoral vein. The profunda was incompletely visualized at its junction with the superficial femoral vein (fig. 5). At operation the common and superficial femoral veins were free. The profunda was occupied by a thrombus whose upper end could be seen when the vein was severed, a short distance from the junction of the profunda with the superficial femoral vein. This corresponded to the venogram. Several of the tributaries were occupied by thrombus. There was no recurrence of pulmonary embolization following ligation.

*Case 4.* (Adm. #496962). Male, 55 years old, developed thoracic pain and hemoptysis eight days after an exploratory thoracotomy. The symptoms were assumed to be related to the

pulmonary lesion until next day when pain in the right calf appeared for the first time, soon followed by pain in the left thigh. There was tenderness in these regions. A venogram revealed block of the superficial femoral vein to a point below the entrance of the profunda (fig. 6). At operation the upper end of the thrombus could be seen when the common femoral vein was severed prior to ligation, the site corresponding accurately with the venogram. There were no further episodes of pulmonary embolization.

*Case 5.* (Adm. #498972). Male, 54 years old, was under hospital observation for sub-acute intestinal obstruction for a period of one week. Pain in the left calf and thigh were then complained of and tenderness was elicited. There was some swelling of the leg. Because of the abdominal condition operation on the femoral vein appeared indicated only if



FIG. 8a. Block of femoral vein, Bauer technique

the thrombosis had in fact extended into the femoral vein. The venogram (fig. 7) revealed this to be the case, the block involving the superficial femoral and profunda veins. At operation the thrombus was found to extend almost to the inguinal ligament at which level the vein was severed and found to be free, directly above the upper end of the thrombus. This case and possibly the following are the only ones in the series of femoroiliac thrombosis in which pulmonary embolization had not already occurred by the time the patient came to operation. In the other cases the pulmonary embolization which had taken place was usually severe as might be anticipated from the size of a thrombus detached from the femoral or iliac vein.

*Case 6.* (Adm. #510238). Male, 58 years old, convalescent from pneumococcal pneu-

monia, developed fever, chills, and dyspnea. Several days later he complained of pain in the left calf and tenderness was noted. A venogram with the Bauer technique suggested block of the femoral vein below the entrance of the greater (internal) saphenous vein (fig. 8a). This was brought out more clearly by the Sussman technique (fig. 8b). The existence of a thrombus at this high level, which was in the nature of a surprise because of the absence of symptoms and signs in the thigh, was confirmed at operation, at which the upper end of the thrombus was seen in the femoral vein immediately below the entrance of the greater saphenous. The convalescence was uneventful after ligation of the femoral vein.

*Case 7.* (Adm. #498494). Male, 27 years old, admitted for the treatment of pneumonia. Five days later the patient was afebrile and allowed out of bed. The next day there was

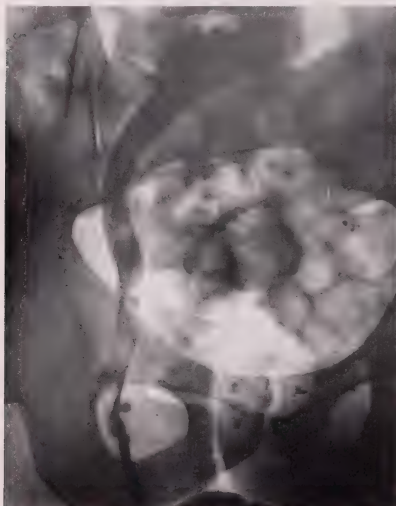


FIG. 8b

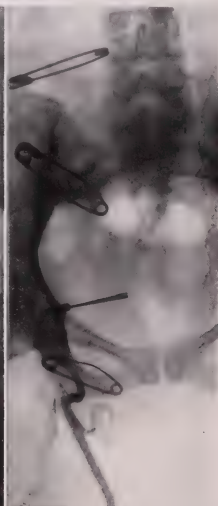


FIG. 9

FIG. 8b. Same case as Figure 8a, employing Sussman's technique  
9. Non-visualization of femoral and iliac veins

severe right pleuritic pain followed in 24 hours by hemoptysis. There were no symptoms referable to the legs but tenderness in one calf could be elicited. A venogram of this leg revealed a defect in the upper femoral vein. At operation the femoral vein was normal at the usual site of section. Traced downwards, the upper end of the thrombus was noted to extend into the profunda. The further course was uneventful.

*Case 8.* (Adm. #503803). Supravaginal hysterectomy was performed on this 41 year old patient. On the fifth post-operative day there were pain and tenderness in the right calf. Two days later pain extended to the inguinal region. Severe right thoracic pain and dyspnea occurred on the ninth post-operative day. There was some discussion as to the extent of the thrombus. A venogram with the Sussman-Bauer technique failed to visualize the femoral or iliac veins (fig. 9). At operation there was a soft thrombus which completely blocked the femoral and iliac veins extending upwards to or beyond the vena



cava level. The profunda and saphenous veins, which visualized in the venogram (q.v.), were found to be free from thrombus at operation. The further course was uneventful.

*Case 9.* (Adm. #515689). This was a case in which the diagnosis of venous thrombosis was not possible except by venography. In any event it was a poor risk patient in whom operation would have been confined to one vein if venography had not demonstrated bilateral femoral vein thrombosis. On the first admission of this 59 year old female the diagnosis of heart failure was made and the patient was treated accordingly. She complained of bilateral calf pain, the film of the chest revealed infiltration in the left lower lobe, the ECG revealed myocardial damage. The patient left the hospital virtually symptom-free. She returned 17 days later, again in heart failure, with dyspnea and orthopnea. The ECG was as on the first admission. *Examination of the legs was negative insofar as evidence of venous thrombosis was concerned.* Venography of the right leg revealed non-visualization of a segment of the common femoral vein; of the left leg, an irregularly and incompletely filled femoral vein up to a normal iliac. These findings were confirmed at operation, the details of which are set forth in the section concerned with operative treatment.

The foregoing cases and others which could be added establish the reliability and precision of venography by the Sussman-Bauer technique in the diagnosis of femoroiliac thrombosis. The contrast with the uncertainties of venographic diagnosis of thrombosis in the calf is evident. Of note is also the fact that there were instances in which the diagnosis of femoroiliac thrombosis was made by venography and could not otherwise have been made. Thus there are occasional indications for venography and no justification for discarding the method. The indication for venography of the calf has been stated. The most important indication for femoroiliac venography exists in a patient who has suffered a severe pulmonary embolism and in whom there is no clinical lead as to whether or not the embolus is derived from the legs or, assuming it to be of femoroiliac origin, from which leg it is derived. There are of course those who believe that a bilateral ligation should be done in all cases to be on the safe side and one may say that there is considerable justification for this view in cases of minor embolization, or in cases in which thrombosis at the femoral level would not be anticipated. However, in the presence of major embolization in which the patient is ill and in which the operative procedure, designed to be life-saving, probably will involve removal of a thrombus from the iliac vein, operation should be confined to the affected leg if, as is usually the case, only one leg is involved. Here the indication for femoroiliac venography is imperative, in my opinion. It is also indicated in cases in which the diagnosis of thrombosis cannot be made clinically. The method should not be employed in those instances in which the patient is too ill to be moved and turned in the various positions required for the cannulization of the vein and the placing of the films.

# ESSAYS ON THE BIOLOGY OF DISEASE<sup>1</sup>

ELI MOSCHCOWITZ, M.D.

## CHAPTER 20

### LAENNEC OR PORTAL CIRRHOSIS

While the distinction between toxic hepatitis or portal cirrhosis is sometimes not always possible, portal cirrhosis differs from toxic hepatitis in the following respects: 1. In portal cirrhosis the process is diffuse and evenly distributed. In toxic hepatitis, sometimes considerable areas of the parenchyma are intact and the portions of liver involved are irregular in distribution. 2. In portal cirrhosis there is a genuine hyperplasia of connective tissue. In toxic hepatitis the connective tissue represents, to a large extent at least, a condensation of the fibrous framework of the organ (1). 3. Etiologically the evidence is very strong, as we shall try to show, that portal cirrhosis is in large part a deficiency disease. Toxic hepatitis, both clinically and experimentally, is caused by poisons; chloroform, trinitrotoluene, arsenic, carbon tetrachloride, phenylhydrazine, phosphorus, cinchophen, salvarsan, etc. Also judging from recent investigations on acute infectious hepatitis in the present war (2) the probability is strong that a filtrable virus is sometimes involved. 4. Most important of all the biology of the two diseases is entirely different. We have already reviewed the biology of toxic hepatitis in Chapter 4. We will now review the biology of portal cirrhosis.

A. *The etiology of portal cirrhosis.* The relation of alcohol to the production of cirrhosis was for long misunderstood, largely because experimentally it was impossible to reproduce portal cirrhosis by alcohol alone. This observation together with the fact that portal cirrhosis occurred frequently in the proven absence of alcoholism, led some to seriously question the causal relation of alcohol to cirrhosis. Nevertheless the high incidence of a history of alcoholism in portal cirrhosis (3 and 4), its frequency in certain occupations in which easy access to alcohol is available (e.g. brewery employees and bartenders) and the decline and rise of portal cirrhosis in this country following prohibition and its repeal (1), cannot be ignored. Thanks largely to the work of Connor (5) and to recent experimental investigation, the causal relation of alcohol to portal cirrhosis is slowly being clarified. Its action is not direct but an indirect one.

It has long been known that alcohol addicts have a deficient food intake. Romano (6) in a study of 131 chronic alcoholics found that nearly a half were on a deficient diet. Of these 79 per cent had a polyneuritis. This accords with the frequent history of polyneuritis due to thiamin deficiency antedating cirrhosis of the liver (7 and 8). The diet is apt to be limited to proteins and fats with

<sup>1</sup> This is the twentieth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph. Ed

little carbohydrate, and poor in certain vitamins especially vitamin B (5). The reasons for the deficient food intake are the following: 1. The high caloric value of alcohol which spontaneously decreases the need for additional food calories. 2. The loss of appetite through thiamin deficiency and in some instances to an alcoholic gastritis. The frequency of achlorhydria in alcoholics has been stressed (4). In the past few years successful experimental reproduction of portal cirrhosis has been accomplished by various types of deficient diets, and although no unitary mechanism has as yet been forthcoming, these results help to clarify much of the obscurity of the pathogenesis of portal cirrhosis and particularly the etiological relation of alcohol.

Chaikoff, Conner and Biskind (9) kept depancreatized dogs treated with insulin alive for 2.6 to 5.8 years and obtained fatty livers which eventually revealed the typical morphological appearance of portal cirrhosis. In the terminal stage the fat content of the liver returned to normal. They found the precise sequence noted in human cirrhosis, namely, fatty infiltration, hyaline degeneration, atrophy of the hepatic cells at the periphery of the lobules, and subsequent periportal fibroplastic proliferation, ending in the typical hobnailed liver. Later Chaikoff and Conner (10) fed dogs on a high fat diet and in three of four animals that lived between 138 and 386 days a fatty liver developed with fibrosis, but these livers differed from the preceding in that the fibrosis was diffuse and not perilobular. Gyorgy and Goldblatt (11) produced fatty infiltration with cirrhosis on diets deficient in vitamins B<sub>1</sub>, B<sub>2</sub> and riboflavin. Later the same investigators (12) produced focal and diffuse hepatic necrosis with fatty infiltration followed by a portal cirrhosis, in rats in 100 to 150 days by a diet of moderately high or a high content of fat but low in casein and choline, both lipotropic factors. Cystine added to the diet aggravated the cirrhosis while supplements of choline reduced the severity and incidence. Methionine, another lipotropic factor, was highly effective in preventing injury. Furthermore these animals revealed effusions into the pleura, pericardium and peritoneum, sometimes even bloody; the effusions possessed a low serum albumin, between 1.5 and 2 per cent. Although the necrosis is central or midzonal the cirrhosis is periportal. Bollman (13) also found a diminution in blood serum protein in carbon tetrachloride poisoned animals and noted that ascites developed only when the serum albumin was low. Blumberg and McCollum (14) produced cirrhosis in rats with a high fat and low protein diet which could be prevented by choline. They also report an accentuation of the cirrhosis by adding cystine but found that the daily addition of 10-20 mgm. of choline or one gram of yeast or both neutralized more or less completely the effect of cystine on the liver. Rich and Hamilton (15) on diets supplemented by vitamins but lacking yeast produced a fatty liver with portal cirrhosis. They determined that the cirrhosis was not due to the lack of vitamins B<sub>1</sub>, B<sub>2</sub>, P<sub>6</sub>, or nicotinic acid. They could prevent the cirrhosis by adding yeast.

Lillie, Daft and Sebrell (16) produced a fatty cirrhosis in the course of a year on a diet low in protein and low in the sulfur containing aminoacids. If alcohol is added the changes are more marked.

Earle and Webster (17) on a diet of which 10 per cent was cystine obtained a

cirrhosis preceded by a hemorrhagic necrosis resembling that observed in eclampsia and followed by fatty infiltration.

Halliday (18) on a basic diet of only 5 per cent fat and 73 per cent sucrose and deficient in vitamin B<sub>6</sub> produced a fatty liver which could be remedied to a large extent by choline.

Gavin and McHenry (19) by adding choline could prevent the development of a fatty liver on a vitamin B deficient diet.

Webster (20) produced fatty livers in rats on a diet poor in protein and choline and rich in fat, which could be prevented by a rich protein diet with the addition of molasses or yeast. The addition of cystine increased the severity of the process.

Fouts (21) produced fatty cirrhosis in dogs fed on a low protein diet supplemented by thiamin, riboflavin, nicotinic acid, pyridoxine and pantothenic acid. The administration of a high protein diet with casein prevented the process. Clinical improvement followed the ingestion of large amounts of choline or powdered liver extract. Evidences of vitamin deficiency disappeared but the fibrosis of the liver persisted.

Spellberg, Keeton and Ginsberg (22) obtained fatty livers and cirrhosis on a diet containing 20 per cent fat—chiefly butter fat. Other fats, for instance hydrogenated vegetable oil (Crisco) did not produce fatty livers, which leads them to believe that it is not fat alone but the kind of fat that impregnates the liver cells that causes damage.

Even in the experimental production of toxic hepatitis the destructive effects may be minimized or entirely neutralized by similar substances. Von Glahn and Finn (23) lowered the incidence of cirrhosis produced by lead arsenate by adding brewer's yeast to the diet. The effect is independent of the glycogen content. Miller, Ross and Whipple (24) gave animals almost complete protection from chloroform hepatic injury by administering methionine and/or, to a lesser extent, cystine before the anesthesia. Other nonsulfur containing aminoacids alone or in various combinations afforded no protection.

From these apparently diverse data these facts can be gleaned—a. That diets deficient in certain substances may produce cirrhosis. This deficiency may be either an unknown member of the vitamin B complex that is contained in brewer's yeast, or the absence of a lipotropic factor, of which the most active are choline, methionine and betaine. The lipotropic action of casein is due to the methionine content (25). Both are independent of the glycogenic function of the liver. Choline cannot exert its lipotropic action on a fatty liver due to a high fat diet, apparently because the fat is deposited too fast; nor does it act on all types of fatty liver; for instance it does not prevent a fatty liver from developing after tetrachloride poisoning, although it hastens the disappearance of the fat (25). The precise mechanism whereby lipotropic substances act is unknown. b. That the cirrhosis is almost in every instance preceded by a fatty change either with or without an accompanying necrosis. This holds true even when a cirrhosis is produced by toxic substances, for instance, phosphorus, carbon tetrachloride and chloroform. c. Protein deficiency alone does not cause

cirrhosis, for cirrhosis can even be induced experimentally on a high protein diet. Apparently, cirrhosis is determined by deficiency of certain amino acids in the protein content that are largely lipotropic in action (26).

As far as these experimental results permit us to say, apparently any method whereby a very prolonged and pronounced fatty infiltration of the liver is produced may in time induce portal cirrhosis of the liver. Fatty infiltration (not degeneration!) resulting from a high fat diet, the absence of a lipotropic factor in the diet or a deficiency in the vitamin B complex alone will not produce cirrhosis; an interaction of these factors is essential plus a sufficiently prolonged period. That a fatty infiltration of the liver represents the initial stage of a portal cirrhosis in human beings is fairly well acknowledged. Connor (5) who has had an unusual experience with alcoholism and cirrhosis describes three stages. The first stage is a fatty liver which develops after prolonged ingestion of large amounts of alcohol during which period little or no food is taken or food which contains protein and fats only. The liver is smooth and large. Because of swelling there may be intrahepatic obstruction of bile ducts with resulting jaundice. In the second stage, the liver is still fatty and larger than normal, but there is a progressive perilobular fibrosis. The liver in this stage may be smooth or slightly lobulated. If the individual lives long enough, the liver is reduced in size and nodular, and fat may or not be present. This change in morphology has been noted in biopsies taken years apart (27). The individual may die from an intercurrent infection or from "beri-beri" heart at any stage so that a pronounced fatty infiltration found at autopsy does not necessarily represent an end stage. It is problematical whether a fatty infiltration of whatever origin, given sufficient time, will eventually develop portal cirrhosis. Undoubtedly the quantitative factor, whether it is sufficient to compress and distort the parenchyma, is a necessary consideration, aside from the continuance of the factor that brought the fatty change about.

Human cirrhosis parallels experimental cirrhosis in its favorable response to a nutritious diet and vitamin B concentrate. Patek and Post (28) found that the survival period after two years of observation was greater than in controls and that the survival period after ascites developed was also greater than in controls. The vascular spiders may even disappear. Connor (5) has determined that an adequate diet plus alcohol will not give cirrhosis, and that in animals it is possible to maintain adequate metabolic equilibrium by proper diet even when large amounts of alcohol are given.

Obviously once new connective tissue has invaded an organ, a complete restitutio ad integrum is not possible. Because the liver has enormous compensatory power, the influence of this new tissue upon the reduction of the parenchyma is probably not as serious as its compressing effect upon the finer portal radicles. McIndoe (29) by corrosion technique and Herrick (30) and Dock (31) by perfusion of human cirrhotic livers, have shown that the vascular supply and especially of the portal system is appreciably reduced, with consequent hypertension in the portal circuit. Rousselot, Thompson, Whipple and Coughay (32) have demonstrated such a hypertension in the living subject. Obviously,



the cure of portal cirrhosis lies in prophylaxis or at least in early recognition. Unfortunately, liver function tests in early stages do not always indicate the presence or degree of liver damage, so that one must depend on pure clinical observation. One awaits with interest mass data on the treatment of early portal cirrhosis by methods based on the prevention of experimental portal cirrhosis.

The relation between dietary deficiency and experimental portal cirrhosis may serve as a possible explanation for the hitherto etiologically obscure non-alcoholic cases of portal cirrhosis. Suggestive in this connection is the high incidence of portal cirrhosis in natives of tropical countries (33, 34, 35 and 39) which has been conventionally ascribed to a highly spiced diet and to absorption of toxins. Rogers (36) in India found an incidence as high as 6.9 per cent; Tyagaraya (37) in Ceylon, 5.6 per cent, mostly among the poor classes. In the latter country the diet of the natives consists of rice, vegetables and dried fruit, and is lacking in nitrogen and certain vitamins. Wang (38) in Manchuria reports 54 cases, occurring mostly in the working classes and in farmers. Stitt (35) remarks upon the frequency of Laennec cirrhosis in the tropics, especially in the Dutch East Indies, Java and Sumatra. Malaria has often been ascribed as a cause of cirrhosis especially in tropical countries, but the evidence is entirely inconclusive (1). Ratnoff and Patek (4) believe that it is more likely that dietary deficiency has been disregarded.

Our understanding of the causal relation of dietary deficiencies to portal cirrhosis is so recent that the elucidation of a history of dietary deficiency has not been as yet practiced on a large scale, but Ratnoff and Patek (4) state that if delved into, such a history is usually found.

The reports of the rare causes of cirrhosis in children are extremely unsatisfactory for evaluation because little attempt has been made to differentiate between the fibrosis following toxic hepatitis and portal cirrhosis. As far as one can gather, most of the reported cases represent the fibrosis following toxic hepatitis.

Inasmuch as the liver is an important storage organ for vitamins, various vitamin deficiencies may result from portal cirrhosis as well as act as the cause. Haig and Patek (40) found that 92 per cent of decompensated cases of portal cirrhosis had vitamin A levels below the lowest normal level. This was accompanied by abnormal dark adaptation. We have already referred to the common evidence of vitamin B deficiency in portal cirrhosis. As another evidence is the increase in pyruvic acid content of the blood, in beri beri (41). In advanced cases, the response to vitamin B therapy may be completely lost. Vitamin C deficiency is not common in portal cirrhosis (1), probably because other organs take up the storage function. Vitamin D insufficiency in portal cirrhosis is manifested by the occasional occurrence of osteoporosis in advanced cases (1). Vitamin K deficiency on the other hand is common in portal cirrhosis, not only because the liver manufactures substances like bile which is necessary for the proper absorption of vitamin K from the intestinal tract, but also because the liver is concerned with the formation of prothrombin which requires vitamin K

for its activation in blood coagulation; and finally, because its function as a storehouse for vitamin K is seriously affected. These factors account in part for the hemorrhagic tendency so common in hepatic disease and particularly in portal cirrhosis.

*Serum proteins and portal cirrhosis.* The finding of a low blood serum albumin in experimental cirrhosis is paralleled in human portal cirrhosis. This was first determined by Gilbert and Chiray (42) and has been repeatedly confirmed (43, 44, 3 and 45). In a large series, Post and Patek (46) found that the serum albumin level possessed a mean average of 2.3 mgm. per cent in patients with ascites, and a mean value of 3.7 per cent in those without ascites. The total serum protein had an average of 6.3 per cent in those with ascites and 7.3 per cent in those without ascites. The globulin fraction was the same in both groups so that the albumen-globulin ratio was reversed. The loss is not due to protein starvation because high protein feeding has no effect on the hypoalbuminemia. Post and Patek (47) in a study of 5 patients found that they remained in nitrogen balance on high protein feeding, although the serum albumen levels did not change. The albumen loss is not primarily due to ascites because such a loss occurs even when there is no ascites; however the formation of ascites of any considerable degree aggravates the protein loss. After withdrawal of the ascites, the loss of protein may be profound, since the ascitic fluid contains considerable protein, varying between 0.1 and 1.7 mgm. per cent (44). Most of this protein represents the albumen fraction. The consensus of opinion is that the hypoalbuminemia is due to the impairment of the normal liver function in synthesizing protein. Indeed a lowering of the serum albumen is common in most disorders of the liver accompanied by considerable destruction of the parenchyma. It occurs even in experimentally induced toxic cirrhosis. Moreover, there is strong evidence that the serum albumen is formed in the liver while the globulins may be formed elsewhere (48).

The prognosis becomes increasingly grave as the level of the blood serum albumen decreases, and clinical improvement is associated with a rise. A rise is also associated with a copious diuresis (46).

The low serum albumen is unquestionably the predominant cause for the ascites, and the not infrequent hydrothorax and ankle edema. Ankle edema has in the past been ascribed to the pressure of the ascitic fluid on the vena cava, but ankle edema occurs even in the absence of ascites, and is directly related to the critical edema level of serum albumen (3).

The hypertension of the portal circuit undoubtedly contributes to the production of ascites, especially if the pressure within the venous loop of the capillaries is markedly increased, which is apt to occur in the terminal phase. However this increment of fluid is secondary, since the diminution of the blood serum albumen antedates any clinical evidence of hypertension of the portal circulation.

The serum proteins have been examined electrophoretically. Luetcher (49) and Longworth, Shedlowsky and McInnes (50) found an increase in the  $\beta$  and  $\gamma$  globulins and a decrease in serum albumen. Gray and Barron (51) found that the abnormality in the electrophoretic pattern depended on the severity of the

disease. The most characteristic abnormality is a large increase in  $\gamma$  globulin and a low serum albumen.

*Latent portal cirrhosis.* Inasmuch as the incubation period of portal cirrhosis is one of years, one may presume that there is a dormant period before any marked clinical manifestations arise. This may be termed the compensated phase, and the only clinical evidence may be an enlarged liver. Indeed the number of cases in which a latent cirrhosis is found at autopsy is a considerable one; according to Ratnoff and Patek (4) in their large collected group, 11 per cent. Of 245 portal cirrhoses, McCartney (52) found a latent cirrhosis in 35.5 per cent. He defined latent cirrhoses as those that were not accompanied by jaundice, ascites or esophageal varices, even when hepatic disease had not been diagnosed clinically. The distribution of the active and latent cases according to decades was identical, but the latent cirrhoses tended to be less advanced than the active group. The livers which showed a more advanced degree of cirrhosis tended to be smaller than those in which the process is less advanced. This was particularly true of those which gave rise to symptoms. An enlargement of the spleen was more frequent in active than in latent cases. Of 167 cases of portal cirrhosis that were observed at post-mortem by Rolleston and McNee (53) 52 per cent were latent.

The question arises whether or not these latent cases would have proceeded inevitably to the terminal phases. The answer hinges upon whether a clinical "cure" of portal cirrhosis is possible even though an anatomical cure is not. This cannot be answered with any assurance. Cases have been reported in which a cirrhosis has remained dormant for many years, but inasmuch as the life cycle of portal cirrhosis is long, one cannot be assured that even such cases might have progressed in time. The problem is further complicated by the fact that portal cirrhosis occurs in the senescent years with its incidental morbidity. Thus it is interesting to note that McCartney (52) reports as the commonest causes of death in latent cirrhosis, heart disease, accident, intestinal carcinoma, pneumonia and cerebral hemorrhage. Even if portal cirrhosis does not kill directly it may be therefore a predisposing cause, since it is well known that such patients are unusually susceptible to infection. Both in latent and active cirrhosis the incidence of fatal pneumonia and other infections is high, approximately 20 per cent (52).

*Relation of estrogens in portal cirrhosis.* Estrogen introduced into the portal system either by organ transplantation or by injection into castrated female animals does not cause estrus (54). In heart, lung, liver perfusion experiments it was found that estrogen was inactivated by the liver (55). Zondek (56) discovered that by mixing liver mash with estrogen that the latter was inactivated. Biskind and Biskind (57) found in vitamin B deficient female rats that there was a markedly diminished activation of estrone in the liver, and recently Singher, Kensler, Taylor, Rhoades and Unna (58) found that in riboflavin and thiamin deficient rats liver slices were unable to inactivate estradiol, while pyridoxin, pantothenic acid, biotin and vitamin A had no effect upon the inactivation. In castrated female rats poisoned with carbon tetrachloride and

alcohol estrogenic substances did not produce activation of the uterus (59). Glass, Edmondson and Soll (60) in all their cases of advanced liver cirrhosis, noted no combined but high free estrogen values in the urine and low or negative androgen values; and they suggested that the gynecomastia and testicular atrophy so frequently observed in advanced male cirrhotic patients were the result of the failure of the cirrhotic liver to inactivate estrogens. Marrison (61) who found testicular atrophy in 57 per cent of 28 cases of Laennec cirrhosis, ascribes the same etiological mechanism. These observations may also account for the frequent impotence in patients with portal cirrhosis.

These observations are of special interest because gynecomastia, testicular atrophy and the smooth skin and feminine distribution of the hair in males with portal cirrhosis have been ascribed in the past as evidences of a constitutional background.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Orchitis and Hydrocele after Cardiac Infarction.* B. Kisch. Am. Heart J., 29: 641, May, 1945.

This case is unique in that, on the sixteenth day after indubitable cardiac infarction, orchitis and hydrocele developed in conjunction with intense abdominal pain. The explanation offered for this picture is embolism due to mural thrombi caused by cardiac infarction.

*Differential Diagnosis of Early Lesions of Venereal Diseases.* B. A. KORNBLITH. New York State J. Med., 45: 623, May, 1945.

The object of this report is to set down the present minimal diagnostic criteria for the differential diagnosis of early lesions of the more common venereal diseases. Clinical criteria are less reliable in diagnosis. The early lesions are essentially granulomas and depend mostly upon the isolation of the individual causative agent for their specific identification. When a primary lesion of the genitalia is observed, the following procedures are carried out first: 1. For the spirocheta pallida, repeated dark field examinations to exclude syphilis. 2. For the gonococcus, repeated smears and cultures to exclude gonorrhea. 3. For the Ducrey bacillus, smears stained by the Unna-Pappenheim stain to rule out chancroid. 4. For spirocheta pallida, and the identification of any microorganisms, or the aspiration for making Frei antigen a "gland puncture". When all these methods are utilized and found negative, the following confirmatory tests should be added: 1. A blood Wassermann reaction to exclude syphilis. 2. Biopsies of local lymph nodes to exclude lymphogranuloma venereum acute lymphadenitis, tuberculosis, metastatic carcinoma, or blood dyscrasias. 3. Biopsies of the local lesions to rule out carcinoma in particular. 4. Aspiration of any pus present to make Frei antigen and to test it on known and control cases. 5. The performance of the known intradermal reactions—the Frei test, the Ducrey vaccine test and the granuloma inguinale intradermal reaction.

*Roentgen Ray Therapy of Mycosis Fungoides.* O. L. LEVIN AND H. T. BEHRMAN. Arch. Dermat. & Syph., 51: 307, May, 1945.

A case of mycosis fungoides is described in order to illustrate the value of controlled radio-therapy in this disease. The patient received 67,000 roentgen units with no discernible toxic effects. The general care and management of this disease is discussed. The technical and detailed aspects of proper administration of roentgen ray therapy in this disease are enumerated. Contrary to the general conception of therapy in mycosis fungoides, we are opposed to the administration of arsenic for this disease for reasons mentioned in the preceding comment. It is to be emphasized that with proper therapy the life span of patients with mycosis fungoides may be appreciably lengthened.

*The Medical Treatment of Peptic Ulcer Refractory to Sippy Therapy.* A. WINKELSTEIN, A. CORNELL AND F. HOLLANDER. Surgery, 17: 696, May, 1945.

The chief point of attack in peptic ulcer therapy is the "acid-pepsin" factor. The usual forms of ulcer therapy, including the Sippy method, are reviewed and their inadequacies are discussed. The principles of the intragastric drip therapy for peptic ulcer are described.

A group of 60 ulcer patients, refractory to the usual medical therapy, were treated with milk-soda or aluminum gel by the Winkelstein intra-gastric drip procedure. Twenty-two of these are presented as examples of the successful application of this form of therapy to refractory peptic ulcer patients.

*Acute Bacterial Endocarditis in the Aged.* F. D. ZEMAN AND S. SIEGAL. *Am. Heart J.*, 29: 597, May, 1945.

In an effort to clarify the disease pictures encountered in the aged, nine cases of acute bacterial endocarditis, with autopsy, have been reported among patients whose ages ranged from 60 to 80 years. In none of these cases was the diagnosis made clinically. The bacteriologic, pathologic, and clinical features are discussed, and it is pointed out that the diagnosis is obscured by the multiplicity of symptoms and signs, as well as by the prostration of the patient. It is believed that these cases will be detected more often if the possibility of this complication is borne in mind, especially when positive blood cultures are found in old people, and even in cases in which the diagnosis seems to be obvious. Clarification of the clinical problems posed by the aged patient offers many fascinating opportunities to the discerning physician.

*Insulin Mixtures in the Treatment of Diabetes.* D. ADLERSBERG AND H. DOLGER. *J. A. M. A.*, 128:414, June 1945.

A review of 1131 diabetic patients of the Mount Sinai Hospital revealed that 46 per cent were controlled with diet alone, while 54 per cent required insulin. In the latter group, 79 per cent were satisfactorily maintained by one daily injection of protamine zinc insulin, 5 per cent by 1-3 injections of regular or crystalline insulin, 3 per cent by one injection of globin insulin and 13 per cent by various mixtures of regular (crystalline) and protamine zinc insulin. Of the 80 patients using insulin mixtures, 44 per cent were on "equal" mixtures, i.e., equal parts of both types of insulin, 35 per cent were on mixtures containing a surplus of protamine zinc insulin, and 21 per cent on mixtures containing a surplus of regular (crystalline) insulin. Insulin mixtures present a decided advance in the treatment of severe diabetes. The advantages are flexibility of the regimen and adaptability to the requirements of the individual. The use of a single stock mixture in fixed proportions deprives insulin therapy of these two advantages and is at present not recommended.

TO

## DR. I. C. RUBIN

THIS VOLUME IS DEDICATED

ON THE OCCASION OF THE

TWENTY-FIFTH ANNIVERSARY OF THE RUBIN TEST

AND IN RECOGNITION OF HIS OUTSTANDING SERVICE

AND CONTRIBUTIONS TO GYNECOLOGY

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TO  
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OUR BELOVED AND ESTEEMED COLLEAGUE,  
WHO HAS GIVEN OVER FORTY YEARS OF  
DEVOTED SERVICE  
TO THE MOUNT SINAI HOSPITAL



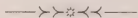
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*A. Rubin*





**W**hereas, **The Mount Sinai Hospital** of New York has been most fortunately graced since 1906, by the inclusion within its medical staff of

**Dr. H. O. Rubin**

recently elevated to the office of Consulting Gynecologist, after his service beginning as Intern and progressing to the highest rank of Gynecologist to the Hospital; and

**W**hereas, during his many useful and fruitful years of endeavor he has, in addition to his multitudinous general services, including his painstaking concern and warm sympathy for all patients under his care, and his great interest in the teaching and development of younger men of his profession, conducted extensive research in the subject of human infertility and has originated a method known to the world by his name, for demonstrating the patency of the Fallopian Tubes, and has perfected conservative operative procedures, and safe methods of diagnosis and accurate treatment in this field; and

**W**hereas, his name, work and reputation are known to and honored by the medical profession in all sections of the globe, Now, therefore, be it

**R**esolved, that this Board of Trustees expresses to Dr. H. C. Rubin its great regard for his professional attainments, its gratitude, and the gratitude of the Hospital for his loyal service and his scientific achievements which have enabled the Hospital and his professional associates to benefit by reflection from his renown, and its deep affection for him as an individual, as a friend, as an associate, and as a warm kindly and considerate human being whose humanity was never dimmed or overshadowed by the lustre of his professional eminence. And be it

**F**urther Resolved, that this Board welcomes Dr. Rubin as the Consulting Gynecologist, and looks forward to many years of further association with him and to his probable further acclaim resulting from future services.

New York, February 19, 1946

*Michael Hollander*  
Secretary

*Der W. Rosenbaum*  
President



## FOREWORD

It is fitting that after more than 25 years of painstaking labor and research in this particular field of gynecology, well deserved recognition may be accorded to their author in the publication of a fitting memorial by his friends and associates. The pages of this volume therefore include the contributions of professional colleagues both here and abroad and their universality serves as an indication of the widespread interest in his attainments.

Dr. Rubin initiated this important work over a quarter of a century ago. He has added to and improved his original procedure, never satisfied that he had achieved a static end. World-wide recognition has been given to the fact that transuterine insufflation now holds an established place as a means of determining tubal patency, primarily in cases of human sterility. The accompanying experiments have suggested many hypotheses both of academic and clinical import. The details of the search for a final determination of the value of the methods may be found in Dr. Rubin's numerous and valuable contributions to the literature as well as in those of other investigators. Criticisms have resulted but these have been largely overcome by the constant efforts to improve the procedure which now, thanks to the care and time expended, has almost reached a stage of perfectionism.

The practical information obtained through the medium of transuterine insufflation has been of enormous importance and of satisfaction both to doctors and their patients, and the American medical profession may be proud of the fact that one of its members has inscribed for himself an outstanding place in its roster.

As Chairman of the Executive Committee, I am pleased to acknowledge the cooperation of those who, by their articles in its pages, have made this volume an outstanding and memorable contribution to American medical literature. Especial commendation is merited by Dr. Joseph H. Globus, the Editor, for his painstaking and laborious work in bringing this memorial to a successful fruition. To Dr. Rubin, it should constitute an enduring evidence of the admiration and good will of his many friends and associates.

GEORGE W. KOSMAK, M.D.





## AN APPRECIATION

It may appear strange that I whose interest in gynecology is only a collateral one springing from my previous tenure as pathologist to Beth Israel Hospital, should be asked to write this introduction. But I feel I am qualified, not only because of an unbroken and warm friendship of over 30 years, but more especially because it was my enjoyable privilege to follow the slow germination of an idea to its ultimate consummation. This began during the period of Dr. Rubin's association with me in the pathological laboratory and I have been a close observer of Dr. Rubin's labors ever since.

There is no need for me to review the steps in the progress of his discovery, from the visualization of the Fallopian tubes with various radio-opaque substances to oxygen insufflation, then to carbon dioxide and finally to the addition of the kymograph which converted this technique into one of the most refined instruments of precision of medical science. Each step represented a technical advance, and most observers would have been content to stop somewhere in the midjourney toward the desired goal. But with the doubt of the scientist and sensitive perception of the artist, Dr. Rubin aimed at nothing less than perfection. Finally after five years of experimental checking and rechecking, the method appeared safe, and with considerable trepidation, was tried in the living woman on November 3, 1919, a date that deserves remembrance in the annals of gynecology.

Visualization of the Fallopian tubes with radio-opaque substances had been done by a number of observers previously. These attempts have been frankly acknowledged by Dr. Rubin in many of his publications, although they were unknown to him when the idea was born in his own mind. The difference between Dr. Rubin and these observers was that he possessed that mental attribute so vital in the pursuit of discovery, namely the follow through. The first radical departure that distinguishes Dr. Rubin's labors from those that preceded him was the use of a gas for tubal insufflation and he has pursued the potentialities of this procedure ever since.

A follow through in meditation is as essential in science as in a stroke in tennis. This indeed is the mental quality that distinguishes scientists of distinction from lesser lights. It is altogether probable that many of the scattered observations that clutter medical writings could be integrated into fundamental laws of medical science by this discipline. Had Dr. Rubin merely perfected the insufflation apparatus, the achievement would have been considerable. But again he followed through and he determined not only its clinical applications in relation to sterility but opened the hitherto comparatively unexplored field of normal and abnormal tubal function. He also discovered some therapeutic potentialities of tubal insufflation, but these still await complete fulfillment. Dr. Rubin therefore deserves acclaim not only because he discovered a precision technique, but particularly because his labors have been so thorough that little

of any consequence has been added by others. This is not the usual history of technical discoveries in science. For the present and probably for the immediate future, Dr. Rubin's observations stand unchallenged.

Even had he not discovered tubal insufflation, Dr. Rubin would have achieved distinction for his other contributions in his chosen field. Since 1910 Dr. Rubin has written two books, one on *Symptoms in Gynecology; Etiology and Interpretation*, (D. Appleton & Co., 1923) and one on *Uterotubal Insufflation*, (Mesby & Co., 1947) and 88 articles. In addition, he has contributed the chapters on sterility in the Curtis system of Gynecology, in the system of Surgery edited by Dean Lewis, and the chapter on uterotubal insufflation in the *Cyclopedia of Medicine* published by F. A. Davis and Co. Of the 88 articles, 33 are devoted to visualization of the Fallopian tubes and uterotubal insufflation. The remaining 55 reveal an unusual versatility. Dr. Rubin has delved into almost every field of gynecology; clinical, operative, diagnostic, physiological and morbid anatomical. His contributions are substantial and while of a lesser magnitude than those devoted to utero-tubal insufflation, they reveal the sound thinker, the keen observer, the student, the critic, the teacher, and the humanitarian. There is not the slightest tinge of propaganda in any of Dr. Rubin's papers nor is he ever a mere encyclopedist. There is a personal touch in all of Dr. Rubin's writings; they are never stereotyped, and the reader can always carry away something new and informative.

It is given to few in our calling to make a first rate discovery and above all to achieve recognition for it during his lifetime. This satisfaction is not only Dr. Rubin's but our own since medical science is richer for his labors and he has endowed gynecology with a method that has appreciably widened its scope. In the essays by his colleagues that follow we are only trying to return to Dr. Rubin what he has given us. They represent but a small compensation for the rich endowment he has conferred, but in all events they serve as a token of our gratitude and admiration.

ELI MOSCHCOWITZ, M.D.

DR. I. C. RUBIN

HIS CONTRIBUTIONS TO THE SCIENCE AND ART OF SURGERY  
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## CONTRIBUTION TO THE STUDY OF TUBAL PATENCY BY KYMOGRAPHIC INSUFFLATION

LOUIS BONNET, M.D.

*Ancien Chef de Clinique à la Faculté de Médecine de Paris*

*(Paris, France)*

By introducing *kymographic insufflation*, in 1925, Rubin considerably improved his method of tubal insufflation. But curiously enough, this improvement was not widely known in France, since it had only been mentioned by him in a short note in 1930 (1). On my visit to New York, in 1934, Dr. Rubin was kind to demonstrate to me how his apparatus worked and to show me certain details which were not included in his description. Convinced of the extraordinary value of this method, I have since devoted a great deal of my time to popularizing it in Europe. My first step was to assemble, in a monograph<sup>1</sup> (2), the details of Rubin's method which were scattered in his numerous communications, adding the details he gave me personally. This study was submitted to Dr. Rubin and he was kind enough to write a preface for it. Having acquired considerable experience, I was ready to make this method known through France (3) and elsewhere (4). Finally for the practical utilization of kymographic insufflation, I constructed an apparatus (5) which has the advantage of being more portable than that of Rubin. Owing to its precision, I was able to make a careful study of tubal stenosis, including calibration of the tubes, followed by a study of the caliber of normal Fallopian tubes. These findings constitute my contribution to kymographic insufflation. The following is an outline of my observations.

### I. APPARATUS

My apparatus (fig. 1), as already noted, differs somewhat from that of Dr. Rubin:

1. The mercury manometer has been replaced by a metallic manometer, which is less bulky and makes the apparatus easier to carry. With the metallic manometer the ordinate axis is slightly curved, but because of the length of the radius the records obtained are very similar to the mercury manometer. This is shown in Figures 2a, b and c, which represent, respectively, records of tubes with normal patency, tubes with non-patency and tubes with spasm. The pen of the recording manometer, always in readiness, records very clear tracings at about half the height of the tracings obtained with Rubin's apparatus.

2. The kymographic drum has a fixed speed (one revolution in 6 minutes). It is worked by an electric motor which is completely noiseless, but which can, when desired, be replaced by a spring motor.

3. *Metric-valve*. The addition of a metric-valve—*completely independent of the flow and stop valve*—is one of the chief improvements which I have contributed

<sup>1</sup> It should be noted that none of the work done by me personally and which is described in the present article, appeared in this book which was published in 1937.

to kymographic insufflation and which has permitted me to obtain accurate results in my studies. With this valve it is possible to provide *instantaneously* a *certain flow* of gas and to change *instantaneously* from one amount of gas-flow to another. This is extremely important, as will be seen later.

The idea of a metric-valve is not as simple as it at first appears, as it involves a certain number of problems in physics. In order that a gas flow be *measurable*, in the exact sense of the word, the gas flow must be *uniform* and therefore practically independent of the pressures recorded during the examination.

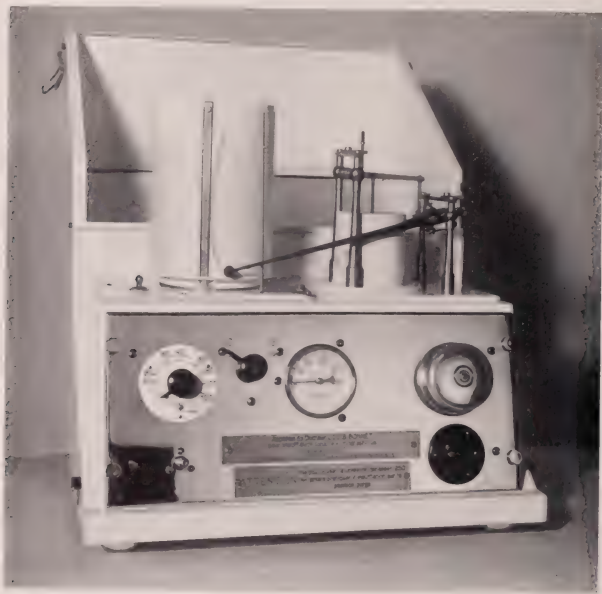


FIG. 1

## II. TONUS OF THE UTERO-TUBAL OSTIA

With regard to the graphs of normal tubes, I shall only emphasize one point, namely, the measurement of the tonus of the utero-tubal ostia.

As soon as a sufficiently characteristic tracing has been obtained (fig. 2a), I stop the flow of gas without withdrawing the uterine cannula, indicated on the tracing by the letter A. After this, no more gas enters the utero-tubal cavity, but the gas which is already there continues to flow through the fimbria: a fall



of pressure is recorded by a descending oblique line. Soon, the pressure is insufficient to keep the utero-tubal openings open. The closure is recorded by a horizontal line. In some cases, the fall in pressure takes place in successive steps, staircase fashion, with one or two intermediate horizontal lines, which correspond to the tubal contractions, during which flow of gas has been stopped.

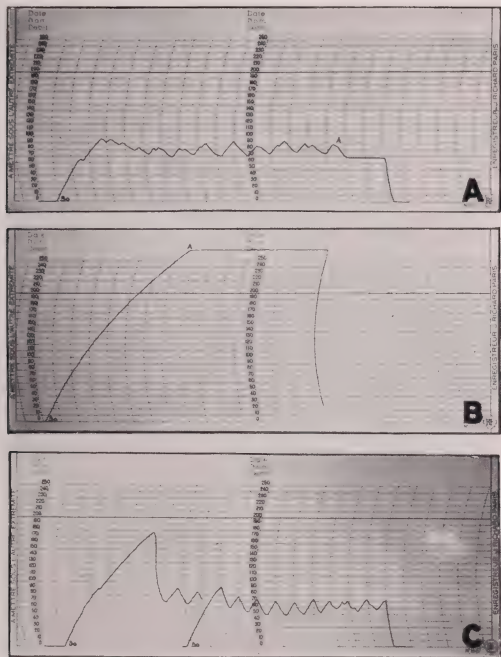


FIG. 2

The pressure represented by this horizontal line, indicating the *closing* of the utero-tubal ostia, is, generally, less than the *opening* pressure. Therefore, it is this closing pressure which is uninfluenced by a possible spasm at the beginning of the test, that I consider as expressing the best measurement of the tonus of the utero-tubal ostia. When a horizontal tracing is distinctly obtained, the cannula is withdrawn and the tracing, once more, falls almost vertically to 0.

## III. STENOSSED TUBES

The term *stenosed* tubes is to be restricted to tubes which, without being non-patent, show a more or less diminished lumen, due either to an internal cause (lesion of the mucous membrane) or to an external cause (peritubal adhesions, twist or bend, etc.).

The study of such tubes was not sufficiently elaborated by Rubin. That is why I have endeavored to develop it further by virtue of the accuracy which my apparatus offers. Stenosed tubes, whose walls have but little flexibility and elasticity on account of inflammatory infiltration or peri-tubal lesions, show, in contrast to normal tubes, a reduced motility, or more often a completely absent

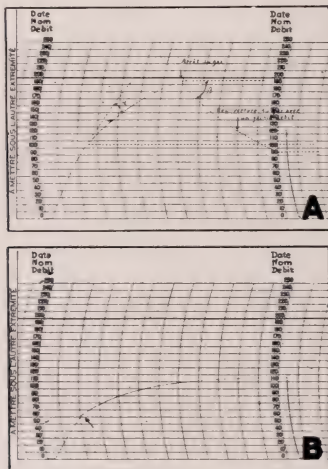


FIG. 3

motility. This is a very important fact, as, under these conditions, stenosed tubes act in the same way as ordinary narrow rigid tubes. As a result I have been able to make an experimental study of the flow of gas through artificial stenoses (fragments of capillary tubes used for making thermometers). The validity of these experimental conclusions applied clinically is proven by the fact that the tracings obtained clinically are absolutely analogous to those obtained experimentally.

It is impossible to review here the entire experimental study (6) of artificial stenoses.<sup>2</sup> I will, therefore, only record one of the principal conclusions. Given

<sup>2</sup> A part of this study has not yet been published but will appear, as soon as conditions permit, together with the other published works in one comprehensive study.

a stenosis of *fixed* caliber, it is possible to find a *certain flow* (the smaller if the stenosis is smaller) for which one can obtain, at a *given pressure*, the tracing of a horizontal line, which I have called the *state of equilibrium*, because, at that moment, there is equilibrium between the quantity of gas arriving in the stenosis and that which flows out. This is possible because the amount of gas arriving is uniform and measurable (a feature of my apparatus) and that the amount flowing out increases with the pressure, as shown in the experimental study. The importance of the conclusions to be drawn will soon become obvious.

Clinical examination of a stenosed tube with my apparatus is done in the following way (fig. 3a):

1. After opening gas at a given flow (as a general rule I begin all my examinations with a flow of 30 cc. per minute), a rise of pressure is recorded as an obliquely ascending line until the pressure opens the utero-tubal ostium (as a rule this opening pressure is higher in the case of stenosed tubes than in the case of normal tubes). I wish to emphasize that if the tube examined is normally patent, it will then record a series of oscillations, indicating tubal contractions (fig. 2a). If the tube was non-patent, the pressure would continue to rise regularly (fig. 2b), until the flow of gas is stopped. But, in the case of stenosed tubes, as soon as the gas begins to flow through the utero-tubal ostium, a change of direction in the tracing is registered. This tracing becomes more oblique and forms with the prolongation of the first tracing a certain angle [fig. 3a ( $\alpha$ )]. In a certain number of cases, a small fall of pressure is recorded, before the change of direction of the tracing, which, in the absence of cervical regurgitation, would indicate that the stenosis is located at the fimbria (the gas suddenly filling a new cavity).

2. As the test is continued, it will soon be noted that, after having changed directions, the record curves in a paraboloid form, i.e. resembling a parabola without being one, since it can, as a matter of fact, become horizontal.

- a) If the stenosis is relatively wide with a given flow of gas, the tracing soon assumes a horizontal line (fig. 3b), which expresses, as we have seen, the "state of equilibrium."

- b) If the stenosis is relatively narrow with a given flow of gas, it will be observed that a horizontal line can not be obtained within the limits of the graph, as the tracing does not curve quickly enough. This horizontal line could be obtained by utilizing a smaller flow of gas, but it is preferable to utilize two other maneuvers, which moreover confirms the passage of a small amount of gas.

3. When the pressure reaches 200 to 250 mm. (a higher pressure should never be used), the flow of gas is stopped. If there was complete non-patency, we know that we would obtain a horizontal line (fig. 2b), but in the case of stenosed tubes, a little gas escapes, with a resulting fall of pressure (the larger the lumen the more rapid the fall). The recording of the fall of pressure forms a certain angle [fig. 3a ( $\beta$ )] with the horizontal line, after which it takes a paraboloid form experimentally and clinically. Experimentally, the recording reaches the horizontal at 0, but, clinically, when the utero-tubal ostium closes, it would become horizontal if the second maneuver were not introduced.

4. Therefore, before the pressure reaches that corresponding to the opening

of the utero-tubal ostium, the gas is opened again, and, by means of the metric-valve, a measured flow is quickly introduced, smaller than the initial flow, and which records the horizontal line indicating the "state of equilibrium" at this pressure (fig. 3a).

*Measurement of the caliber of the stenosis.* This is an entirely new subject, which has not been studied before. Three elements of the above tracing can be utilized for measuring the caliber of stenoses.

1. The angle  $\alpha$  (fig. 3a), formed by the change of direction of the tracing, is not precise, as it is relatively small and varies with the flow utilized, therefore, I have not used it.

2. The angle  $\beta$  (fig. 3a), formed by the tracing and the horizontal line, is much more interesting, because it varies within far greater limits than the preceding angle. This angle (absent in the case of non-patency) immediately gives an idea

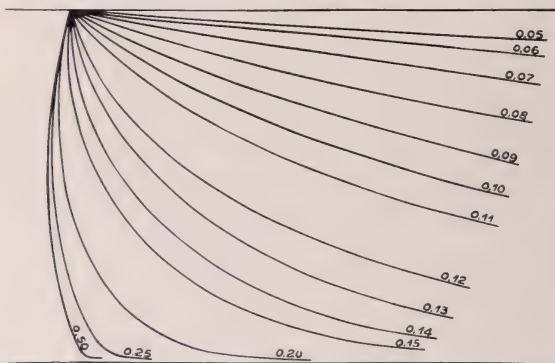


FIG. 4

of the degrees of the stenosis, but as the fall of pressure, after the gas has been closed, is recorded in a paraboloid curve, the angle varies with the pressure. Therefore, instead of measuring this angle, it is preferable to compare the clinical recording obtained with a series of graphs obtained experimentally with calibrated artificial stenosis (fig. 4).<sup>3</sup> The comparison is obtained by superimposed tracings, but, of course, it will not be exact unless the tracings are recorded on the same scale and with the drum revolving at the same speed. A measurement of the diameter of the stenosis to a hundredth of a millimeter is thus obtained. I wish to add that with this procedure, the measurement of the caliber is independent of the amount of gas utilized for insufflation.

3. The procedure based on the recording of the "state of equilibrium" applies

<sup>3</sup> These recordings have been obtained with tubes of 2 cm. in length; the length being a factor, I arbitrarily chose the mean length of 2 cm.

more generally and more accurately since it permits measurement to a thousandth of a millimeter.

The flow of gas in a narrow tube is an extremely complex physical problem, but when the flow is uniform, as is realized at the time of the "state of equilibrium," it is then governed by Meyer's formula (7), to which Fortier (8), when studying the viscosity of gas by its flow through capillary tubes, recently added several corrections and has helped me with his advice. This formula<sup>4</sup> is complicated and the calculation of the diameter of the stenosis would be extremely difficult. Therefore, for practical purposes, I have standardized a series of tracings (fig. 5), with which, given the amount of flow and the pressure of the "state of equilibrium," one can obtain, by merely reading, the diameter of the stenosis to a thousandth of a millimeter. The pressure is read on the ordinate

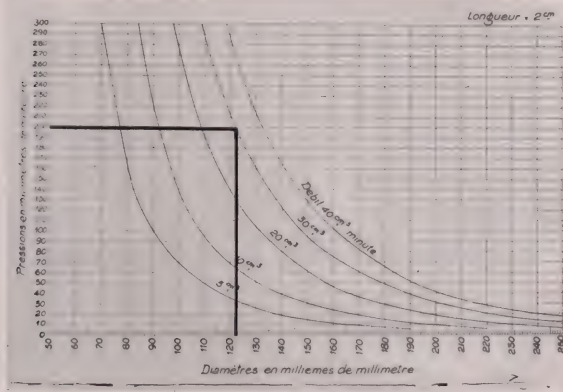


FIG. 5

axis, the curves correspond to the flow (the intermediary flows are easily determined) and the diameter is read off on the abscissa.

The accuracy of this procedure, which can be surprising, is however easy to verify, when it is concerned with artificial stenosis, by comparing the figure thus obtained with that obtained by microscopic examination.

In the case of tubal stenosis, the caliber found could be applied to both tubes, but we know that if one of the tubes is not patent or stenosed, and the other normal, a recording of normal patency is obtained. It would appear that in most cases when stenosis is recorded, it would apply to the tube that is the less involved, the other being generally completely closed.

<sup>4</sup> The formula which I have utilized is published in *Gynec. & Obst.*, 40: No. 5, 1939-40, and in the Thesis "Jugiau," Paris, 1939.



Finally, I wish to make it very clear that when speaking of diameter, I do not refer to the anatomic diameter of the stenosis (which would not be true because of the great irregularity of the lumen of the Fallopian tube), but to the diameter of the cylindrical tube with which a tracing similar to that recorded clinically can be obtained experimentally.

*Results of measurement.* Measured in the aforesaid manner, the diameter of the stenosed tubes vary between  $50^5$  and  $150\ \mu$ . From a practical point of view, it can be said that stenosis is very narrow between 50 and  $90\ \mu$ , fairly narrow between 90 and  $130\ \mu$ , and above these figures, wide.

*The importance of the measurement of the diameter of stenosed tubes.* The measurement of the diameter of stenosed tubes is extremely significant as it

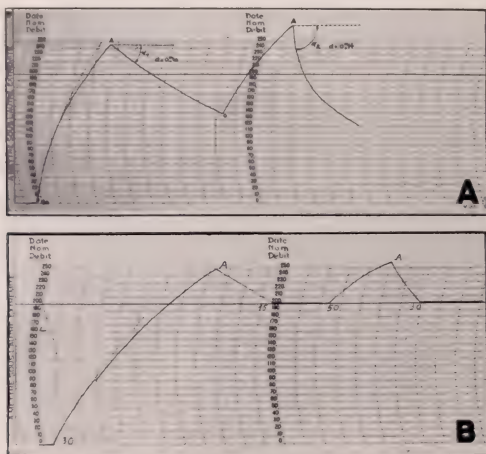


FIG. 6

enables us to easily determine any improvement obtained in caliber, either during one insufflation, or after another insufflation, for example, after diathermic treatment.

During insufflation one may, as a matter of fact, ascertain an improvement in the caliber of a stenosis. On the tracing of Figure 6a, it will be noted that on the second test, after turning off the gas, the fall of pressure is more rapid than during the first test. On referring to the experimental tracings of Figure 4, it will be noted that the caliber passes from 0.10 mm. to 0.14 mm. Likewise, the tracing of Figure 6b also shows an increase in the diameter of the stenosis. After the second stoppage of gas, the fall in pressure is more rapid than after the first, and

<sup>5</sup> Below  $50\ \mu$ , the measurement seems to be fictitious.

the "state of equilibrium" is obtained after the two consecutive tests at a pressure of 200 mm., with the flow 15 cc. in the first case and the flow 30 cc. in the second case. Figure 5 shows that the diameter has increased from 100 to 122  $\mu$ .

The measuring of the diameter of stenoses is particularly important in cases of sterility. In fact, if by repeated insufflations, and especially after diathermic treatments, improvements of stenosed tubes may proceed to normal patency, though this is admittedly very rare. Now, when a tube remains stenosed, we know, from practical experience, that it is, as a general rule, unfit for fecundation. The measurement of the diameter of the stenosis gives us the explanation. It has been noted that the diameter of these is between 50 and 150  $\mu$ , and it is not difficult to understand that the ovum, having a diameter of 200  $\mu$ , can not pass, especially as in such cases as we have seen, the tubes have neither elasticity, flexibility nor motility.

*Stenosis and spasm.* In order to ascertain the part which spasm could play in the case of stenosed tubes, I have studied, with Atlas (9), the effect of antispasmodics. We have used papaverine and other synthetic antispasmodics (perparine, papaveryl, syntaverine, etc.), injected intravenously during the test. Out of 17 cases, 14 remained unchanged and in only three cases did we obtain an improved passage of gas, in one case even attaining the recording of slight oscillations at the end of the examination. This shows us that in some cases there may exist, in addition to stenosis, a more or less important spasmodic element; but that, in the majority of cases, organic lesions transform the stenosed tubes into rigid canals. Moreover, the therapeutic effect of antispasmodics appears to be very slight, for even in the case of spasms, which diminish after the injection of an antispasmodic, these spasms recur, in general, a few moments afterwards.

#### IV. MEASUREMENT OF THE CALIBER OF NORMAL TUBES

The study of the caliber of stenosed tubes would have been incomplete if I had not also included calibration of normal tubes, or to be more precise, the narrow portion of the tubes (about 5 cm. long) formed by the junction of the intramural and isthmie portions (10). The problem is different, for it is no longer a question of rigid canals, as in the case of stenosed tubes, but on the contrary one of canals which are the site of contractions recorded as oscillations (fig. 2a).

In order to take these measurements, I used:

1. The tracing of the fall of pressure after the stoppage of the gas (the latter operation is indicated by the letter A on the tracing).
2. The descent line of the oscillations.

1. By employing the first method, we find ourselves working under the same conditions as for the examination of stenosed tubes after the stoppage of the gas. In both cases, we record a regular fall of pressure, but in the case of normal tubes, the tracings of Figure 4 can not be used, as the latter were established with a length of 2 cm. The element of length plays a part in the escape of the gas through narrow tubes, and as we have in this case not only to take into account

a length of 5 cm., but also larger diameters. I was obliged to set up a new series of tracings.

2. With regard to the second method, the latter tracings, in turn, cannot be used. Conditions are indeed different, as during the recording of the descent line of the contractions, injection of the gas is continued with a certain flow (in general 30 cc. per minute) and if we record a fall in pressure, it is because the quantity of gas escaping through the fimbria is greater than that being injected into the tubes. If granted this fact, new experimental tracings become necessary.

As the contractions are irregular, I have taken the tracing corresponding to the largest diameter obtained by either one of these methods from a large number of tracings of normal tubes.

Under these circumstances, I was able to ascertain that the *total* caliber corresponds to a diameter of 230 to 500  $\mu$ . I wish to reiterate that with a cylindric tube 5 cm. long, having a diameter of 230 to 500  $\mu$ , a tracing absolutely analogous to those obtained clinically can be recorded experimentally. Normal contractions may be imitated by the rhythmic tightening and relaxation of a rubber tube placed immediately before the capillary tube.

*Existence of two tubes.* The above mentioned caliber represents a *total* caliber, for, there are two tubes. At first sight, we might wonder if the diameter of each tube is not half the total diameter. This, however, is not the case. In fact, one must take into account that the flow of gas into a narrow tube is directly proportionate to the fourth power of the diameter. The result is that the relation between the diameter of each identical twin tube, functioning as regard the outflow of gas in the same manner as one single big tube, is 1 to  $\sqrt[4]{2}$ , or from 1 to 1.19 or thereabouts, i.e. that the difference is relatively small. This very interesting fact can be experimentally verified with the aid of two tubes connected with a Y-tube. We can demonstrate, for example, that two tubes of 270  $\mu$  can function as a single tube of 320  $\mu$  (given the same length).

Under these circumstances, if the total diameter varies between 230 and 500  $\mu$ , the result is that the diameter of each of the tubes varies, in round figures, between 200 to 400  $\mu$ . It should be stated that this diameter represents a minimum diameter, as it is assumed that the two tubes are equal, while in reality one might be larger (and the other smaller or even non patent). On the other hand, on account of the elasticity and the contractions of normal tubes, the diameter thus ascertained is probably smaller than that which is functionally utilizable.

In conclusion, we can now understand why the ovum (which has a diameter of 200  $\mu$ ) cannot pass through a stenosed tube, while on the contrary, it can pass through normal tubes. This correlation of physiological and clinical facts demonstrates that the above figures—without assigning them a fixed value—must approach the truth.

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## ON CONSERVATION OF FUNCTION IN GYNECOLOGY

VICTOR BONNEY, M.D., M.S., B.Sc., F.R.C.S., F.R.A.C.S., F.R.C.O.G.

*Honorary Fellow of the American Gynecological Society*  
*[London, England]*

Surgery, otherwise a handicraft, has been raised to the graciousness and dignity of an art by an ideal, the nature of which has changed as the surgeons' resources have grown, until the sheer saving of life, regardless of subsidiary consequences, has given place to a far greater aim, the cure of disease or deformity coupled with the maintainance or the restoration of function. The ideal finds its fullest expression in modern orthopedic and plastic work, but gynecology, ever since Marion Sims closed a vesico-vaginal fistula has been active in the field, and of recent years the principle of conservation has been extended to include certain major conditions affecting the uterus, ovaries, and tubes, which previously did not come within its orbit.

Indeed of all parts of the human body the female reproductive apparatus stands first in psychological, social and national importance, and there, if anywhere, surgery's highest ideal should be pursued.

Radical extirpation of a uterus, ovary or tube which is functional or capable of having its function restored is an admission of surgical defeat against which the mind of every earnest surgeon naturally rebels; and the object of this paper is to show that the number of such defeats can be very substantially diminished.

### EXTENDED MYOMECTOMY

Very early in my career I began to be dissatisfied with the ruthlessness of the then accepted surgical treatment of fibroids. To have to remove the womb from a quite young woman on account of half a dozen entirely innocent tumors, seemed to me the very bankruptcy of surgery, and I began to try to do better. Many surgeons before me had attempted to extend the scope of myomectomy; most notable of all, Alexander, of Liverpool, whose name the Alexander-Adams operation commemorates. This surgeon in 1897-98 wrote three papers in which he enunciated what are still the fundamental principles of extended myomectomy and reported the removal of as many as 25 fibroids from a single uterus. The resources of surgery and the mental attitude of the surgeons of that day were not ripe for such an advance; the seed he sowed fell upon stony ground, and myomectomy remained, for many years afterwards, an operation of very limited scope.

The great bar to its extension was the danger of hemorrhage, for until some means could be found to control bleeding, during what must often prove a prolonged operation, the procedure was fraught with risk.

I made my first definite essay in extended myomectomy in 1912, and in the years following tried out many devices for temporarily controlling the blood flow through the uterus. But I found that the circulation up the cervix is so free, that clamping both ovarian and both uterine arteries, or even, instead of the



last named, both internal iliac arteries, does not abolish the circulation through the uterus. I then devised a clamp which not only blocks the uterine arteries but compresses the cervix as well, and this instrument (combined with clamping

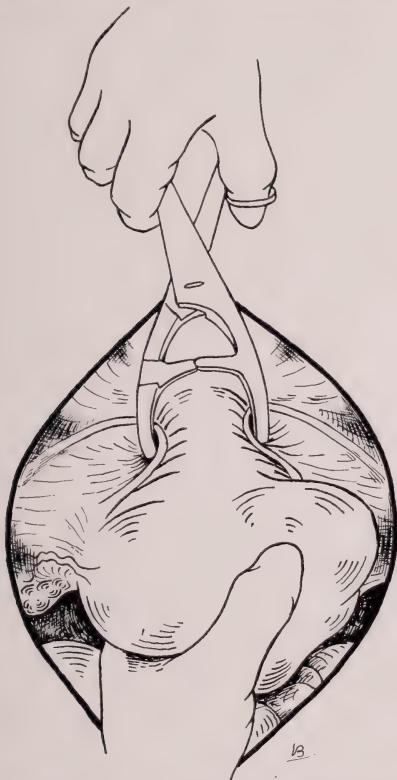


FIG. 1. Usual application of the myomectomy clamp. The blades should be covered by rubber tubing but this is not depicted in the illustration.

the ovarian arteries) has removed the menace which for so long hindered the development of the operation.

It is true that, without the use of the clamp, not all extensive myomectomies are accompanied by profuse bleeding, but the surgeon is unable to distinguish

beforehand the cases which are going to bleed badly from those that are going to be kind to him, and the threat of hemorrhage heavily weighs the scale against the conservative operation.

The clamp is ordinarily applied with the angle between the blades and the shanks opening downwards, though sometimes it goes on better in reverse, but,



FIG. 2 Reverse application of the clamp. Rubber tubing not shown

whichever position is adopted, one thing is important: *both round ligaments should be included in the grip*, for otherwise the jaws slip down the conical cervix below the level of the uterine arteries. It has been suggested that the clamp may injure the vessels and promote thrombosis, but 25 years, use of the instrument has proved these fears to be groundless.

Next in importance to the prevention of hemorrhage is the realization that the uterus, left behind after the enucleation of fibroids, is always, and sometimes greatly hypertrophied, so that it needs cutting down and refashioning before it is returned to the pelvis. Involution occurs after myomectomy as after labor, (but less vigorously) and therefore the replaced organ should be slightly larger than normal.

It is not within the province of this paper to describe the technical steps of the operation, and the variations which have to be employed to meet the differing arrangement of the fibroids in the uterus, for I have recently in another publication minutely dealt with these.<sup>1</sup> Unlike hysterectomy, there is no standard operation of myomectomy and each case has to be dealt with on its own peculiarities. The scope which this affords to ingenuity makes extended myomectomy one of the most interesting operations in all surgery, and on that account alone it should interest every abdominal surgeon confident of his own powers.

Up to the present, however, it has received relatively scant attention. Rubin in 1942 epitomised the American literature on the subject during the last 40 years and, even with the British literature added, it makes a very meager total compared with the voluminous writing on hysterectomy, much of which, has of late concerned itself with the degree of destruction the operation should effect. It suggests that, in general opinion, myomectomy on the large scale is too difficult and too dangerous for the ordinary surgeon to undertake. That this is entirely wrong will be shown by a brief epitome of my own results.

Up to January, 1945, I had personally performed myomectomies 806 times. The fibroids were solitary in 40 per cent and multiple in 60 per cent of the cases, and the largest number of tumors removed from a single uterus was 225. There were 9 deaths in the series; an operative mortality of 1.1 per cent.

The disturbed conditions which obtained in England during the war and which still continue, have prevented keeping in touch with my more recent cases, but in 1937 I published the results of a follow-up of 379 of the patients whose operations had been performed sufficiently long before to warrant a useful estimate of their remote results.

New fibroids had appeared in nine cases (2.3 per cent) and, making full allowance for the possibility of others having appeared since the investigation, it is certain that my recurrence rate is under 4 per cent. To achieve such a result it is absolutely necessary to remove every fibroid down to the smallest seedling. Menorrhagia, without recurrence of fibroids, either persisted or appeared subsequently seven times.

Of the 137 patients who were married, within the childbearing age, and wishful to have children, 52 or 38 per cent conceived subsequent to their operations; and only one of these women miscarried, the rest being delivered of live children.

It may be objected that the experience of a surgeon, who has devoted much time and thought to a particular operation, does not prove that it will be equally successful in the hands of those whose practice of it has been much less.

<sup>1</sup> The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy. Cassell & Co., London. Hoehler & Co., New York.

My reply is that the methods I have employed call for nothing beyond ordinary surgical ability, and that determination alone is needed to place extended myomectomy in the repertory of every surgeon whose province includes the female generative organs; not, mark you, as a substitute for hysterectomy but as a fair surgical alternative, whenever conservatism serves the interest of the patient best.

#### ADENOMYOMECTOMY

It occasionally happens that, the abdomen having been opened to perform myomectomy, the surgeon finds to his surprise, not a fibroid but an adenomyoma. What is he to do? Must he perforce remove the uterus? Not at all; the condition is an entirely innocent one, and the growth, unless very large, can be excised leaving the greater part of the uterus *in situ*. I have performed the operation on and off during the last twenty-five years. All my patients recovered and, as far as I know, there has been no recurrence in any one of them. This result proves that these growths are purely innocent and, incidentally, discloses the interesting fact that endometriosis of the uterine wall is a phase, not a habit of the endometrium.

#### OVARIAN CYSTECTOMY

Twenty years ago I succeeded in enucleating a dermoid cyst from out the ovary and, pursuing the implication, I was able eight years later to record a number of such operations, and announce that all innocent cysts (dermoid cysts, follicular cysts, chocolate cysts, and adenomatous cysts) were enucleatable, besides certain solid tumors such as fibromata and granulosa-cell tumors.<sup>2</sup>

I have by now performed the operation over 300 times and it is a singularly safe procedure, every one of my patients having made a good recovery. I began by applying it to small cysts only, but, having gained confidence, I now employ it for large cysts as well, whenever the age and circumstances of the patient are best served by conservatism.

In 1937 I published the results of a follow-up of 90 of these cases and only in one of them had recurrence taken place, and even of this one I am not sure, as I was unable to obtain particulars of the operation. Of the 90 patients there were 40 who, being married and of childbearing age, desired children and of these 16 conceived after their operations. Five of the pregnancies occurred after the enucleation of chocolate cysts (bilateral in 2); six after the enucleation of serous cysts (bilateral in 2); four after the enucleation of dermoid cysts (bilateral in 2); and one after the enucleation of a solid granulosa tumor.

As with myomectomy, the war has prevented a further follow-up, but I may cite 2 cases subsequent to 1937. From the first of these I enucleated six dermoids (three from either ovary), and from the second five dermoids (three from one ovary and two from the other). Both these women have had two children since their operations.

<sup>2</sup> I have not had the opportunity of enucleating an arrhenoblastoma but shall certainly do it if opportunity offers.

It became necessary to coin a name to distinguish this conservative operation from ovariectomy, in which the whole ovary is removed. I chose "ovarian cystectomy" as aptly conveying what the procedure effects. I have described elsewhere the technique of the operation<sup>3</sup> and will not repeat it here. I venture to believe that a proceeding which enables so important an organ as the ovary to be conserved is a definite advance in gynecological surgery.

It goes without saying that the slightest suspicion of malignancy bars the operation, nor is there any point in performing it on women past the menopause.

#### RESTORATION OF TUBAL PATENCY

It is fitting that, in a publication designed to commemorate the great service Rubin has rendered to gynecology, my final comment should deal with the restoration of tubal patency, of which his work is the foundation.

For a number of years before the introduction of tubal insufflation I had treated hydrosalpinx by making a new stoma, ignorant of the fact that the essence of hydrosalpinx is that both ends of the tubes are closed. Naturally, as regards subsequent pregnancy I had no successes, and I expect other surgeons had the same experience. Rubin's discovery altered all that and I designed an intrauterine nozzle, like a Hegar's dilater, with a disc on it two and a half inches from its upper end, so that the nozzle could be kept fixed in the uterus by the pressure of gauze packed into the vagina against the disc. By this device the effect of blowing air or gas into the uterus can be watched through the abdominal incision; while if air is blown down the tube from its outer end, and any of it reaches the uterine cavity, the needle of the manometer will rise.

In 1937 I sent a *questionnaire* to 55 patients whose tubes I had reopened and received thirty-seven replies. Seven of them had conceived as follows: after external salpingostomy, 2 cases; after reimplantation, 2 cases; after external salpingostomy on one side and reimplantation on the other, 1 case; after double reimplantation and double external salpingostomy, 1 case; and after partial tubal exsection and anastomosis on both sides, 1 case. My proportion of successes, therefore, was 18 per cent; not a figure to boast about, though somewhat better than many which have been published.

It has been stated that, of tubes so operated on, practically all were found to have closed again within a year. This does not accord with my experience, for some of the pregnancies I have cited materialised at periods up to four years after the operation. Just recently a colleague of mine tested, by lipiodol, a patient, both of whose tubes he had reimplanted five years before and found both of them patent; and only last week pregnancy was reported to me in a patient both of whose tubes I reimplanted four years ago.

I have not myself made subsequent tests of the tubes I have reopened. My excuse is a purely sentimental one: if reclosure is demonstrated it takes from the patient the happiness of hope and leaves her poor indeed. I trust the recording angel will drop a tear on this, my dereliction from scientific austerity.

It must be owned however that, making every allowance for changes in the

<sup>3</sup> Ibid.



tubal mucosa, or the ovaries themselves, as the result of pelvic inflammation, the small percentage of successes is a great disappointment. But I deprecate defeatism; rather should our successes, few as they are, act as a stimulus to improve our technique. Consider the amazing resolution to reach the uterus that the ovum sometimes displays. My colleague Louis Bivett excised both tubes in their entirety. A suture in one cornu penetrated the uterine cavity, and endometrium spread along the suture track and projected on the peritoneal surface like a very small caruncle. Pregnancy occurred through this suture track. Such cases teach us to keep our hearts up. I have tried several devices to prevent reclosure, and at present favor the passage of a thin strand of nylon gut down the length of the tube and left *in situ* there, with its ends projecting half an inch beyond the inner and outer ostia respectively. I have found that the strand is spontaneously passed into the vagina in two or three weeks time.

It seems to me that our poor results are probably due chiefly to a grossness in our technique, ill fitting the delicacy and smallness of the parts we operate on. The younger generation, following in our footsteps, and ardent to advance our great art, will surely better what we have done, and on this belief my faith in the future is founded.

## PRELIMINARY HEMOSTASIS AS AN ADJUVANT IN THE CONSERVATIVE SURGERY OF THE UTERUS

PABLO E. BORRAS, M.D., F.A.C.S.

*Associate Professor of Gynecology*  
(Rosario, Argentina)

The brilliant age of anatomic surgery for gynecological disease was soon eclipsed when the sequelae of mutilating surgery began to be observed in these organs.

Biological advances, especially the experimental verification of the close utero-ovarian relationship, confirmed the observations of the gynecologists who had carefully studied patients following the removal of the uterus or of the ovaries. The degenerative lesions in the ovaries persisting after a hysterectomy have been observed by many authors and today there is no doubt as to the future of any ovary which has been deprived of its correlative gland, that is, the endometrium. Cirio and Murray have corroborated the sclerosis and the hyperluteinization of the ovaries after hysterectomy. In the same way, the removal of the uterus in animals used for assays causes functional abnormalities with corresponding organic lesions in other glands (hypophysis, mammary glands, suprarenal cortex, thyroid). These changes indirectly show the influence of the endometrium on other glands. Hence, there is a great necessity for every gynecologist to understand the functional exigencies of the whole organism, due to age, somatic type, endocrine equilibrium, and other factors. These diverse functions have to be taken into account in the case of any patient who has to undergo surgical intervention for a gynecologic disorder inasmuch as functional disturbances necessitate functional surgery and therefore conservatism. Nevertheless, the term "conservative surgery" is too broad, especially when it refers to the uterus. For some it is conservative when it is not mutilating, that is, when by means of technical artifice part of the organ is saved; for others, when the function of reproduction is conserved; and lastly, for others when it is possible to retain the menses. I believe that the last opinion is more in accordance with the truth. Without the function of reproduction the endocrine equilibrium can be correctly maintained and the patient may not suffer any trouble. On the other hand, without the menses it is very difficult for a woman to maintain her glandular status in perfect condition. Regular menstrual cycles show, as a rule, a good functional state of the uterus and ovaries. Therefore, the physician should make every effort to preserve the menstrual function in every woman who has to be submitted to a gynecologic surgical procedure.

The first radical attempts intimidated the surgeons to a certain extent, for the statistics demonstrated that morbidity and mortality were much higher in the minor interventions than in the mutilating ones; therefore after the first attempts they turned again to anatomical surgery, as a rule simple and of a very precise technique with immediate and very good results.

Searching for the motives responsible for the failure of Conservative Treatment, it was seen that the inconveniences and difficulties were due to the nature of the organ itself. Since every hollow organ always presents greater technical obstacles in its surgery, the physician must possess more surgical skill and is as a rule more exposed to a great number of complications.

Nevertheless, in the surgery of the uterus one difficulty was greater than all others, namely, the profuse hemorrhage which was produced by the smallest cut in the organ, even in the middle line. This was responsible for the enormous difficulties that the surgeon was faced with. The latter, finding himself continually disturbed by hemorrhage, could not locate the bleeding vessels and could not correctly remove the different layers of tissue. The surgeon seldom remained satisfied, since, besides the doubt as to the future of the operative intervention, the extreme rapidity of technique demanded by the economy of blood loss and the hurried work on surgical fields full of blood, very seldom satisfied him. In addition, the surgeon lived in fear of the necessity for further operations and exploratory laparotomies. The layers of the organs wrongly exposed, the conveyance by the blood itself of septic elements which were in the cavity of the uterus and the small coagulums which remained between the walls of the incision, caused infective pelvic processes, generalized infections and embolism. Phlebitis appeared very frequently 5 or 8 days after the operation, and the surgeon was uneasy until the appearance of menstruation subsequent to the operation.

Considering all these questions I supposed that the hemostasis previous to any operation on an organ such as the uterus, which receives its sanguine current through vessels anatomically well situated and of easy reach, could not be a difficult matter. Thus arose the technique of the preliminary circulatory block, which in the beginning I believed to be original, for I had seen nothing similar in the Argentine nor in the gynecological services of Europe or in America, and I believe I have known a great number of them. Nevertheless, when my assistant, Dr. Rafael Pineda, was about to report the first results of this technique, we went through all the literature within reach and found that in Pozzi's *Gynecology*, page 328, third edition, he already mentions something like it. Also, Blair-Bell in his book "The Principles of Gynecology", page 685, fourth edition, publishes the technique recommended by Bonney and which is based on identical principles, restraining separately, with the appropriate rubber-clamps, the infundibulum, pelvic and round ligaments.

I have up to the present employed preliminary hemostasis in 132 cases of myomectomies and enucleations. There are never any great difficulties in carrying it out, and under those conditions, it is possible to accomplish any plastic operation, however difficult it may be, working at ease and without haste on a uterus completely exsanguine.

Sometimes, with very soft myomas, it is necessary, when the first cut has been made, to compress the uterus to "empty" it of all the blood that might have remained inside. I am never worried about the opening of the cavity and I

apply, at most, a small amount of merthiolate or sulfanilamide. In the two cases of a young woman and an unmarried girl, where the menstrual function had to be preserved above all, I extirpated half of the uterus, dissecting on one side the uterine artery and laying it afterwards on a subperitoneal bed.

In another case, an isthmic nodule forced me to section the uterus when I intended to dissect it. Having joined the ends of the vessel, I made the proper repair. In neither this case nor in the former was there any difficulty.

I have had many opportunities for carrying out myomectomies and enucleations in the most varied and capricious implantations of uterine tumors. I have also performed many varieties of fundic hysterectomies with no other complica-

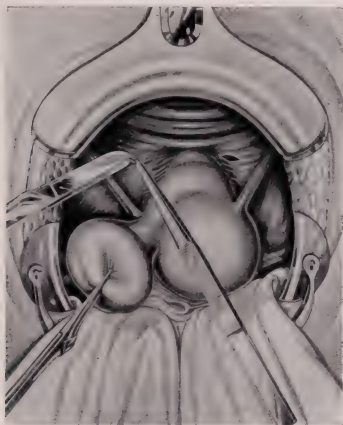


FIG. 1

tions than a parametritis and phlegmon of the broad ligament which yielded in a few days. In both cases, which were amongst the first to be operated on, I had to perform ample myomectomies with several enucleations. I found it difficult to repair the organ, with all its elements, but the processes yielded in short time, without leaving sequelae and obtaining the desired end from the functional point of view. Since the use of penicillin we have had no complications. Rubin, who calls preliminary hemostasis a procedure of the tourniquet has extirpated as many as 33 uterine "myomas" with continuous hemostasis lasting for one hour. The principle on which the method is based is very simple. Two holes are made in the broad ligament at the height of the isthmus of the uterus one centimeter to each side of the same (fig. 1).

A very thin rubber tube, such as those used as tourniquets when an intra-

venous injection is given, is passed through the holes behind the uterus and with a Kocher clamp, the tips of the tube are suitably tightened until the arterial current from the uterine arteries is stopped (figs. 2, 3 and 4).

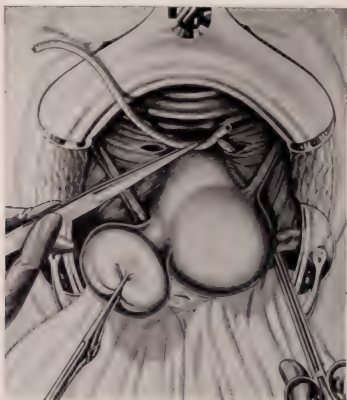


FIG. 2

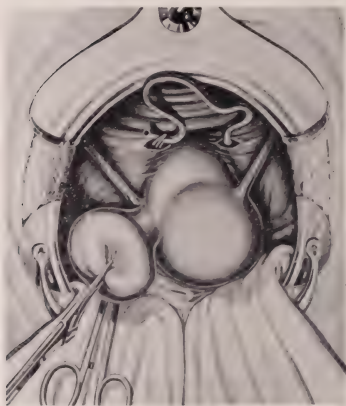


FIG. 3

Professor Castaño has substituted for the rubber tube, a thin massive rubber such as is used by children for their slings. These rubbers are very elastic and less apt to traumatize on account of their small size.



Two ordinary clamps with curved blades of identical resistance in extension and with racks for adjustment, are immediately used (fig. 5).

These clamps (whose blades have previously been covered with a rubber tube with an opening in proportion to the thickness of the clamp in use) are placed on

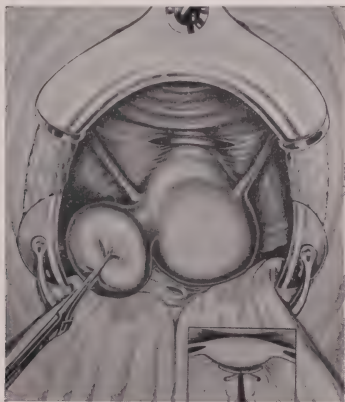


FIG. 4



FIG. 5

both sides of the uterus with their curves outwards. They serve to clamp off the utero-ovarian, the tubal, the round and the broad ligaments in the part nearest the uterus thereby causing the point of the rubber clamp to reach the hole through which the rubber that presses the isthmus has passed (fig. 6).

By means of these clamps every arterial current which flows into the uterus through the utero-ovarian artery, the internal tubaria, the innominate artery

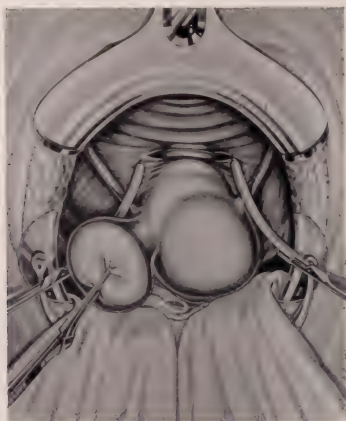


FIG. 6

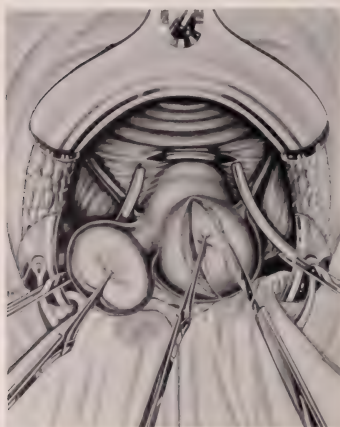


FIG. 7

or inferior tubaria or arterial arch of the broad ligament) and the artery of the round ligament is inhibited.

In this way the uterus is completely exanguinated and is in a much easier and practical condition to work on (figs. 7 and 8).

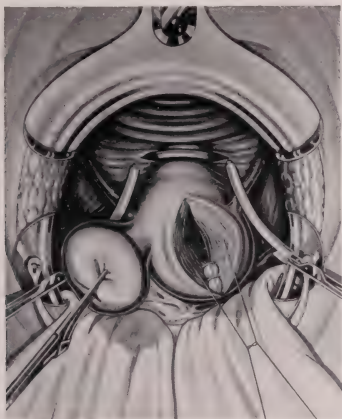


FIG. 8

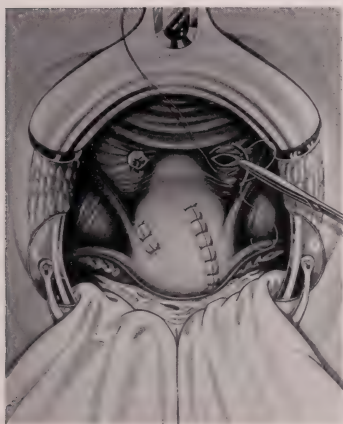


FIG. 9

It has been said, that with such perfect hemostasis, it is not possible to know where bleeding occurs and therefore the necessary ligatures are not made.

Nevertheless, it must be remembered that the uterus does not bleed through large vessels but through very fine arterioles which divide and anastomose without being individualized.

Only the fundic artery must be borne in mind, and as a means of precaution it is convenient to perform a compressive fold round it. Even if the two surfaces of the incision are tightly sutured, the hemostasis is already produced. Besides, if an isthmic or a supra isthmic node has to be extirpated then the rubber clamps and the tie which goes through the broad ligament are loosened, it may be seen how small a blood loss is produced by any of the isthmic-arteries. Sometimes, not always, one or more deep stitches are necessary.

When the hemostatic elements are withdrawn one can immediately notice how the uterus fills with blood, and the stitches of the suture become tense as if a greater effort was demanded. I have made the uterus resist a  $1\frac{1}{2}$  hour block without noticing any circulatory abnormalities in it, afterwards having taken away the clamps and the rubber, one proceeds to close (by a fold) both holes in the broad ligament. It is also possible to transfer the peritoneum from one hole to the other placing it on the interior face of the uterus, covering the sutures according to Pestalozza's technique in hysteropexia (fig. 9).

#### SUMMARY

Surgery of the female generative organs has gone through different stages.

Anatomic surgery spread rapidly at first, and with time displayed all the results of mutilating operative procedures.

Great enthusiasm for conservative surgery followed this period, but soon declined owing to postoperative accidents. Nevertheless when, through biological viewpoints, the importance of the "endometrio ovarica" correlation was established, new techniques were found in order to avoid the distant consequences of mutilating surgery. New types of incision, new therapeutic discoveries, blood economy and surgical expertness allowed a higher category to conservative surgery. In spite of all, when the loss of blood was eliminated through preliminary hemostasis during the surgical procedure, the importance of this technique was only then established.

The advisable technique consists in placing a rubber tube through both broad ligaments on their base, compressing the uterine artery against the isthmus and placing 2 rubber-clamps against the internal tubal artery. In this way the arterial blood supply to the uterus is cut off.

Under these conditions it is possible to dissect miomatous nodules, perform myomectomies, fundal hysterectomies and hysterectomies with extirpation of "intracavitaries" tumors. Thus it is possible to perform, with great care, the most delicate uterine operations thereby fulfilling the most elemental precepts of conservative surgery.

## THE EFFECT OF WAR ON MALE FERTILITY

CECIL COGHLAN, M.B., F.R.C.S., F.R.C.P.I., D.G.O.

[*Sydney, Australia*]

The study of sterility should not be divided into sterility in the male and sterility in the female as is done in most textbooks, but should be "The Study of Childless Marriages," where both partners to the marriage share equal responsibility for the lack of children until the investigating physician has ascertained the cause and allotted the blame.

I still receive many cases where the female partner has had extensive investigation including tubal insufflation, salpingographs and even operative treatment, and the male partner has had no investigation whatsoever. My practice for many years has been to refuse any case where both partners do not come forward.

As a result of this my records up to the end of the year 1941 showed that the male was the probable cause of the sterile marriage in approximately 30 per cent of cases, the female in 60 per cent, and in 10 per cent the cause could not be ascertained, or both were to blame.

In the early part of 1942 after Japan entered the war, the Australian Military Forces who had been serving in the Middle East returned and were given home leave. Some of these men were anxious for their wives to conceive before they left to fight the Japanese. When pregnancy did not immediately occur they came along to find the reason why. In sixteen successive cases I found that the male was at fault, the sperm examinations performed by Drs. Shipton and Sherman showing either aspermia or oligospermia. These men were all fine healthy types, but their departure to the New Guinea front prevented any follow up. From time to time I had a few cases back on leave until early 1944 when the return of the 9th Division from Egypt resulted in a number of disappointed couples coming in to see me. The examination of the male again disclosed, almost universally, aspermia or marked oligospermia.

These findings worried me so much that I wrote a letter to the Medical Journal of Australia in the latter part of February 1944 asking if other practitioners had noticed the same conditions in members of the military forces, and for the help of the military authorities in ascertaining the cause. I suggested that a probable factor was lack of vitamin E, as answers of these men to questions as to the nature of their diet suggested this. I had a number of replies from Australian practitioners reporting similar findings, but no help from the Military Authorities.

In the following tables an analysis of the sperm counts in 150 successive cases is given.



## ANALYSIS OF SPERM COUNTS\*

TABLE I

*Number of sperms present per c.c. Normal over 80 millions*

None.....	in 26 cases	approx. 17%
Under 10 Millions.....	" 40 "	" 27%
Between 10 & 25 Millions.....	" 34 "	" 22%
" 25 & 50     "	" 33 "	" 22%
" 50 & 80     "	" 12 "	" 8%
Over 80 Millions.....	" 5 "	" 4%
Total.....	150 cases	

TABLE II

*Abnormal forms present. Normal number under 20%. (Normal forms 80%)*

Under 20%.....	17 cases	approx. 12%
Between 21% & 40%.....	35 "	" 24%
" 41% & 60%.....	22 "	" 14%
" 61% & 80%.....	28 "	" 18%
Over 80%.....	22 "	" 14%

TABLE III

*Motility. Normal 80%*

None.....	44 cases	approx. 29%
Under 20%.....	18 "	" 12%
Between 21% & 40%.....	13 "	" 8%
" 41% & 60%.....	10 "	" 6%
" 61% & 80%.....	19 "	" 13%
Over 80%.....	20 "	" 14%

From the foregoing tables I would consider that only 30 per cent have any chance of becoming fathers.

The general examination of all these men did not disclose any condition which could account for these counts. Very few admitted to venereal infections and only a very small proportion had pus cells in the seminal specimen. As to treatment I put all the cases on vitamin E and gave them instructions about diet.

Since the end of the war I have still continued to get poor counts in most returned men and war prisoners, and have had a chance to have repeat counts done. In very few have I had improvement, some counts have even been worse.

\* In Tables II and III only 124 cases are considered as 26 cases shown in table I had no sperms present.

For simplicity I have considered a normal count:—

80 million sperms per c.c.

80% Normal forms in count (20% abnormal)

80% Motility.

This is to be expected if the cause was lack of vitamin E as this causes degeneration of the spermatogenic cells of the testicle.

In the last few months I have noticed further, that the wives of returned men who have become pregnant have had an abnormal number of miscarriages. Investigation disclosed no reason in the female and the Rh. factors were compatible, but a sperm examination disclosed poor counts in every case.

I regret that I have not had an opportunity for a biopsy in any of these cases. This would go a long way towards deciding whether vitamin E has been a factor.

This matter is of great national importance, for it means that a large number of the nations best type of young men will be unable to have families. Countries such as Australia are in such need of population, and the best type of immigrant is the baby. It is also sad if these young men who have given freely of the best years of their life for their country are deprived of the greatest of all the joys of life—that of becoming a father, and for the wives also to be deprived of woman's ambition—motherhood.

## PLASTIC OPERATIONS FOR SEXUAL AMBIGUITY

(GYNANDRYNES AND ANDROGYNES)

G. COTTE, M.D.

*Professor of Gynecological Clinic, Faculty of Medicine, the University of Lyon  
(Lyon, France)*

Surgical intervention, designed to repair malformations of the genital tract causing a state of sexual ambiguity, brings up not only technical problems of surgery but problems of a judicial, moral or religious nature. They deserve, in each particular case, special study before one makes a decision. In his excellent book "*Les Hermaphrodites et la Chirurgie*" Ombredanne, having conferred with high officials of the court and the ministers of the different religions, gave an excellent account of the subject. I do not want, therefore, to come back to this question and I limit myself to a report of three observations which are not without interest in regard to the re-establishment of the possibility for adequate sex behavior.

Among malformations of the genital tract, commonly classified under the main heading of hermaphroditism, the first two cases would fall into the category of gynandrim and the last one into that of androgynism.

### CASE REPORTS

*Case 1.\* History.* The patient was declared a boy at birth and considered as such up to April, 1939, when at the age of 16 years he presented a hematuria of three to four days' duration for which his parents had him examined at the Lyon Clinic. In reality it had been the patient's first menstrual period.

*Examination.* This adolescent, although with a boyish hair cut, had a feminine physiognomy. The configuration of the pelvis and of the legs as well as the breasts were those of a girl in puberty. The hair of the pubis had feminine disposition. The external genital organs, which were poorly developed, were of the masculine type. The scrotum was small but of normal form with transverse wrinkles. The bursa was empty but on the right side. In the inguinal canal there seemed to be a small tumor. The penis, which was small, measured about 3 to 4 cm. It was implanted at the normal place, provided with a foreskin, somewhat exuberant, which covered the small glans with a small terminal opening at the top of the organ which did not measure more than 2 to 3 millimeters in length. At the base of the glans another opening terminating the urethra and producing a hypospadias was found. Behind the scrotum the perineum had a masculine aspect. It was solid and resistant, and between the scrotum and the anus there was no outline of a vagina. On rectal examination we found behind the pubis a small mass which might be the uterus.

*Course:* At operation, uterus, salpinx and ovaries were normally constituted. The exploration of the vesico-uterine region did not permit me to recognize the malformation. I therefore decided to puncture the fundus of the uterus with one of the tubestrocar which I habitually use in performing biopsies of the endometrium through the uterine wall. Through the tube I introduced in the uterine cavity a fine Hegar bougie and I observed that after the cervix uteri there was a vagina. After that, taking a small catheter of hard rubber, I introduced it through the tube in the uterine cavity and could see that this catheter found its

\* Published in *Gynecologie et Obstétrique* in 1941, under the title *Gynandroïde à Scrotum Fermé et Petite Verge*.

way through the urinary opening, which was for me proof that there was a communication between the vagina and the urethra. I then closed the abdomen and then cut into two equal parts the scrotum and the perineum on the midline and opened the urethra all its length up to the section before the anus. The urethra then represented a mucosal shred one centimeter large and the wall was sutured to each side of the corresponding hemi-scrotum so as to make two labia majora.

Some days later the result was such that we could then reduce the size of the penis, due in great part to the exuberance of the foreskin. I circumcized the patient and inserted by suture the remainder in the superior part of the re-constituted vulva cleft. Having recognized in the course of this intervention that the urethra opened on the anterior part of the



FIG. 1a. Gynander with closed scrotum (before intervention).

b. Same subject after intervention. Inversion of the clitoris, establishment of the vulva cleft at the posterior extremity in which one sees the vaginal opening.

vagina only a few millimeters above the vaginal opening I tried to unbridle the vagina as far as possible toward the anus so that its entrance was easily accessible.

The result was excellent. Morphologically I succeeded in changing the external genital organs from their masculine type into the feminine. Then I succeeded in constituting a vulva. The vaginal orifice was located about two centimeters from the anus. The urethral meatus, not visible in the picture, opened on the anterior wall of the vagina two to three millimeters above the vaginal opening similar to the feminine hypospadias of Schröder. Functionally, the patient urinated as a woman, straddling instead of urinating in the position she had before intervention, as a boy. The patient urinates in a straight stream without deviation by the walls of the vaginal orifice. The vagina is of normal length but the para-uterine spaces are poorly developed. The dilation is easy. Without anesthesia we easily introduced a Hegar bougie #15. With ethyl chloride narcosis we arrived at #20. Then, with diathermy and progressive dilation, we arrived at #30.

I have to add that the patient, who up to then had been educated as a boy but whose tastes and character adjusted itself badly with her comrades at school, without knowing exactly why, is very happy that her sexual ambiguity has disappeared. There has been a rectification of her civil status.

From that moment on, the patient, whose latent femininity could not express itself, has been living as a woman. After the first sexual intercourse she became pregnant, and this gave us the opportunity to see her again as a patient. The pregnancy developed without incident. We were however in doubt as to whether the delivery could be done in a natural way. There was a flat and generally small pelvis; the soft tissues with reduced dimensions of the perineum seemed to us as contraindicating a spontaneous delivery without producing irreparable damage to the urethra or the rectum. To avoid this accident the patient was hospitalized at the Obstetrical Clinic (Professor Rhenter), where on March 9th a cesarean section was performed without incident. On March 11, under spinal anesthesia a well constituted girl, weighing 3,600 grams, was delivered. In July, 1946, she gave birth to a second girl. Delivery was performed by cesarean section without incident.

*Comment.* This report does not need any commentary. It appeared to me interesting enough to be published by reason of the two pregnancies which occurred after the surgical intervention of the external genital organs. From the surgical point of view as well as from the judicial and moral, the intervention has given satisfaction in all respects.

*Case 2. History.* A young woman, 25 years of age, did not seem to be preoccupied by her malformation. She was menstruating at thirteen and one-half years of age. The periods were painless and lasted four days. She consulted us because of the absence of the vagina.

*Examination and course.* At the examination the patient had a feminine sex. She grew up in the country with instincts and occupations of a girl. The observations of our first case report led us to suppose that behind the perineal wall there was a uterus and vagina which opened into the perineal portion of the urethra. This patient had female sexual characteristics, she menstruated. It was important, therefore, to find the outline of the vagina and to establish its opening into the skin. The first surgical intervention was made on June 24, 1945. The vulvar cleft was brought out to a length of 5 centimeters, stretching out of the spread urethra on its inferior aspect. At the posterior extremity of which we found the outline of the vaginal cavity stenosed about 1 centimeter from the opening, a stenosis which was easily dilated up to Hegar's bougie #16. On July 16, under spinal anesthesia a laparotomy was performed in order to observe the condition of the internal genital tract. There was a uterus and salpinx, which were somewhat hypoplastic. A catheter introduced in the fundus of the uterus showed that it came out on the level of the split urethra. This minuscule vaginal orifice was preceded by a rudimentary hymen. Vaginal dilatation was performed up to #18 and a rubber drain was left in the vagina in order to produce a continual dilatation of the vagina.

The patient was re-admitted to our service on September 19. She had regularly continued the dilatation so that at present she could easily be catheterized with Hegar bougies #24 and 25. But the vulva orifice was still very narrow. Because of this the musculus constrictor vulvae were cut on the midline and brought down the vaginal mucosa which was then fixed at the skin of the perineum. More superficially, to give the vulva a more normal aspect, the hood of the clitoris was resected and the stump inverted.

*Comment.* In this case the problem was simple because there was no mistake in declaration of the civil status at birth. We were dealing with a patient in which the secondary sex characteristics were those of a woman and in whom the morphological aspect of the external genital apparatus and the absence of a



vagina created a state of sexual ambiguity. By a relatively simple intervention we achieved the creation of a vagina and thus gave her the possibility for satisfactory sexual behaviour. We have just learned that this patient is married and has been pregnant for 3 months.

*Case 3. History.* The patient, aged 22 years, consulted my colleague, Professor Santy, because of the congenital absence of a vagina. She was declared at birth to be of female sex. She was brought up as a girl and learned the trade of dressmaking. At the age of 18 she was operated upon for a double inguinal hernia. In the course of this intervention the surgeon removed 2 small nodules which proved on histological examination to be testicles. At the age of 20 the patient consulted a physician because she was not menstruating, and in view of her marriage she consulted us at present.

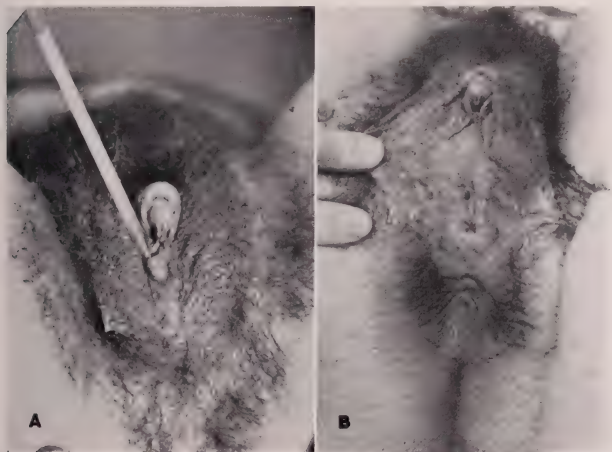


FIG. 2a. Gynander with hypospade meatus with small penis before the intervention.  
 b. The same after inversion of the clitoris, establishment of the vulvar cleft in which one sees the orifice of the urethra and below the opening of the vagina.

*Examination.* The patient was found to be of tall stature, and her general morphology was rather masculine except for the hair which was poorly developed. On the breast there were no mammae but only an areola with small nipples on each side.

On examination of the perineum a rudimentary penis was found on the base of which was an opening of the urethra. Below, between two genital folds, there was a fold corresponding to the perineal urethra. No doubt we were dealing with a cryptorchid subject (the examination of the nodules removed 4 years ago permits this conclusion), with absence of a scrotum and a vulvaform hypospadias.

*Course.* Operative intervention opened many grave problems. Here we were dealing with a masculine subject, neutral at present because of the resection of the atrophied testicles but in regard to the civilian status the subject had already been considered as a girl. She was engaged in feminine work and how could she accept all of a sudden the status of a

boy; more so because she had met a boy of whom she was very fond and to whom she revealed her malformation and who was willing to wait until she was operated upon and then marry her.

In regard to the sex, the subject has a feminine behaviour and, as Ombredanne has very justly said, one cannot impose the male sex on a subject who is not menstruating, who has no penis and who is incapable of having sexual intercourse as a male. It was therefore thought advisable to create a neo-vagina. The subject being declared as a girl or female, there was no objection to her marriage because marriage consists only of uniting two individuals of different sexes. The question may be asked whether a surgeon performing a plastic operation, does not aid in deceit by hiding a deformity which involves sterility and which may later be the cause for divorce. The patient, on the other hand, declared that if she was not operated upon she would commit suicide. From the moral point of view her friend knew that she had no vagina, no uterus and that she would never have children but he accepted these conditions. It was therefore decided to intervene.

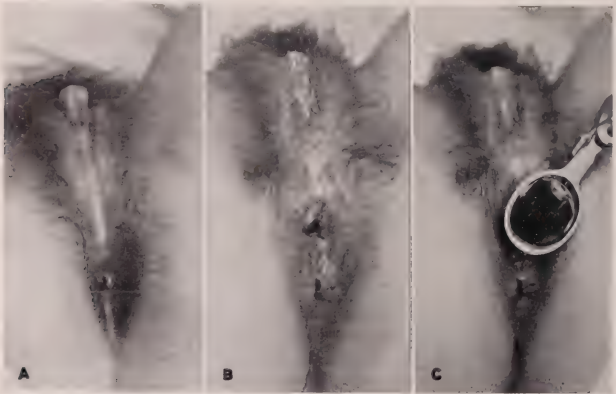


FIG. 3a. Androgyne with hypospade meatus of the penis with rudimentary penis.

b. Creation of a new vagina with the method of Schubert about 2 centimeters in front of the anus. Opening of the urethra in all its perineal length and inversion of the penis of which one can see only the glans.

c. The neo-vagina is easily permeable.

On April 18, 1945 a neo-vagina was performed according to the method of Schubert, with transplantation of the anus, liberation by coccygeal way of the rectum, exclusion of the inferior segment and implantation of the rectum at the level of the sphincter. On May 11, 1945 we started dilatation and continued it easily up to #20. On May 22, 1945 autoplasty of the perineal region was performed such as to give a more feminine aspect, opening of the urethra in all its length with suture of the genital walls and inversion of the penis.

The picture shows this region after operation. One sees about 2 centimeters above the anus the opening of a vagina which measures the depth of 10 centimeters. It is elastic and provided with a mucosal lining.

At present the patient is married. The sexual intercourse is easy and the two parties declare themselves very satisfied. At the moment of orgasm it seems that in our patient there is a slight secretion of fluid, probably prostatic, through the urethra.

*Comment.* The foregoing observations seem to me significant enough to be described because they show how surgeons are capable of modifying malformations and thereby ease their effect upon the psyche.

## A RADIOLOGICAL STUDY OF UTERINE EVACUATION

JEAN DALSACE, M.D.

(Paris, France)

Twenty years have elapsed since hysterosalpingography was introduced, yet it has failed to develop according to early expectations. It appears to me that gynecologists were so satisfied with this method from the outset that further improvement seemed unnecessary. There is no doubt, however, that we do not derive from this method all the clinical and therapeutic advantages it could logically provide. Should we blame the method, the equipment, or rather a certain *laissez faire* attitude? Let us confess that gynecological radiography is far behind other radiographic techniques of hollow organs.

The equipment should be simple and should permit a perfect adaptation of the acorn tip and the cervix. There seems to be general agreement as to the necessity of using a cannula with a short bend. We do not follow other authors who advise that the beak should be introduced up to the internal os. We shall give the reasons later. The speculum should be removed because its shadow may obscure the reflux of the injected substance. There is still some discussion as to whether heavy or light lipiodol should be used. We prefer heavy lipiodol which is slower in its evacuation and outlines the cervicoisthmic region more distinctly. It would be interesting to evaluate substances of even thicker consistency for the study of this region (see publications of Palmer).

We then have at our disposal equipment and a substance which should permit accurate diagnoses. If this is not the case it is due to the fact that gynecologists utilize only a fraction of the possibilities of this method and particularly because they too often use a non-physiological technique. Except for the control method of Cotte most pictures are those of utero-tubal filling and they have an undeniable value. They show the outlines of the uterine cavity (which we must not forget is a real one) and the outline of the tubes. But what gastroenterologist would be satisfied with a barium enema or filling the stomach under pressure—for such cavities are not real ones?

But that is what we do every day. We add to the causes of errors due to pressure, those due to adaptation and the pinching of the cervix which produce abnormal contractions. The pinching of the cervix is by reason of traction and pushing may even change the form of the uterus; if the cervical portion is long and elastic, even the anatomical relationship of the organ may be changed. This fact is easily verified. It is important, and this fact should be emphasized, to exert traction or push so as to determine the fixity of the uterus and its relationship with the tubes which are more or less free in the abdominal cavity. If we can obtain much information from proper uterine filling from pictures taken serially, what should we say about the almost always neglected data obtainable from a study of uterine evacuation?

Gynecologists and radiologists are almost always satisfied with one or two

pictures of filling and one control picture. What gastro-enterologist would be satisfied with one picture of the duodenal bulb? What urologist would be content with a single picture of the urinary tract? Yet that is what we too often do.

It is important to study in detail the uterine evacuation with serial pictures. For many years we have with Ledoux-Lebard and J. Garcia Calderon succeeded in showing how to utilize this study in an economical way. A simple square is made of rubber or metal foil from which a central orifice is cut, thus permitting with a film of 30 by 40 cm. to take four excellent pictures of evacuation.

The *cassette* so manufactured contains a square of Lyshölm which permits

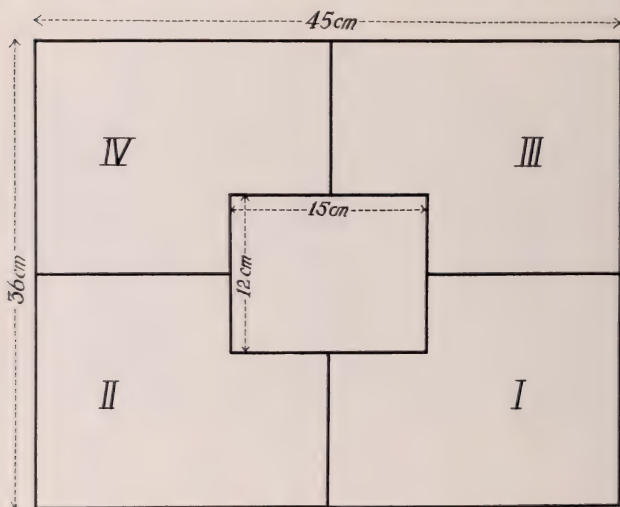


FIG. 1.

a satisfactory focus and yields neater pictures which is easier to interpret. On this square is placed a lead layer in the center of which a rectangle is cut out 12 by 15 cm., sufficient to encompass the pictures of the uterus and the adnexa. One can thus take four successive pictures on a film 24 by 30 cm. by placing each one of the angles of the covering in the transparent rectangle.

We advise taking the first film while leaving the catheter in place. A second film is taken immediately after removing the catheter and permits the observation of anatomical changes which this catheter may have imposed on the uterus. A third film is taken about 1 minute later. At this time the *cassette* is removed and fluoroscopic examination made. In certain cases of delayed or slow evacua-

tion it might even be very diagnostically useful to perform a vaginal examination under fluoroscopy, which would permit more complete knowledge of the relationship of the uterus and the tubes, and the degree of flexion of the fundus uteri on the cervix. In other cases it might be advisable to put the patient in a Trendelenburg position to observe the residual lipiodol in the cervix or in the corpus uteri. At other times, an x-ray film taken in an upright position would yield valuable information. Finally, a vaginal examination under fluoroscopy will help in case of tubal permeability to more rapidly spread the lipiodol which would avoid control x-ray. The comparison of all these evacuations with filling the films permits a study of the utero-tubal physiology and pathology from a new point of view. We shall next examine the findings presented by this study in regard to the problem of sterility and its differential diagnosis.

#### STERILITY

It seems that most gynecologists, when they study sterility by means of x-rays, investigate only tubal patency. If mechanical sterility were always of tubal origin, it would be preferable to perform kymographic insufflation (Rubin's method) which gives us much more precise data on the degree of patency of the salpinges and their peristalsis than the lipiodol. That is to say, of their functional value we can learn more from lipiodol, if we know how to use it, than from insufflation and a careful study of the films will permit us to see zones of dilatation and atresia, to evaluate moniliform tubes, to see pictures with residue, and to understand the origin of certain tubal atresias (for instance deformities of extra-salpingiar origin, adhesions), of which insufflation could not give us the slightest information. We must insist that information should be given by control pictures made at short intervals (which must include evacuation pictures) in all cases of hydrosalpinx. One may also draw from these studies information about prognosis. One can thus obtain knowledge about the tubal musculature, whether the salpinx empties itself or whether the lipiodol remains. We saw cases in which the lipiodol remained in the salpinx for several months. In these cases lipiodol becomes a foreign body and may light up an old hydrosalpinx. In these cases we should advise early salpingectomy. On the other hand a rapid evacuation of the lipiodol contained in the tube will give advance information of a good result of a stomatoplasty or a stomatotomy. But we are wrong to believe that mechanical sterility is always of tubal origin and a well done hystero-graphy will show us that there are many other causes. Let us recall the causes due to a uterine malformation, a septum of the uterus, small fibroids or polyps of the cornua uteri.

There are physiological causes: hyperkinesia or sometimes hypokinesia of the uterus or of the tubes. But more often than one realizes, we are dealing with a cervico-isthmic cause.

*Sterility of cervico-isthmic origin* is much more frequent than is generally admitted and only a study of the uterine evacuation will permit its proper recognition. There may be a simple kink at the level of the isthmus of the uterus, ante or retro-flexion or in latero-flexion which approximate the border of the



uterus with the corresponding border of the cervix often exaggerating these dimensions.

In these cases lipiodol remains and forms a kind of residue which may last for several hours. This explains well the mechanism of menstruation in two episodes which we have described elsewhere. One understands easily that the menstrual blood may go out under a certain pressure, but that the ascension of spermatozoa may be hampered by this kind of obstruction and particularly by the residual secretions which may remain permanently (it brings to mind certain profuse discharges which cannot be explained by non-existent hydrosalpinx). The study of the uterine evacuation in sterility permits frequent



FIG. 2. Hysteroграм, in a case of sterility with sessile polyps of the uterus and cystic salpingitis.

observation of other types of atresias by scars resulting from application of Filhos or even from diathermo-coagulation improperly carried out or improperly performed dilatations.

Sometimes we deal with very long and tiny cervixes, often in the shape of a bayonet which explains the excellent results obtained in the treatment of sterility by a large stomoplasty. One often discovers in the course of the uterine evacuation the presence of a small cervical polyp unobserved during the filling, but appearing during the evacuation. We will return to this point in studying the procedure and its applications.

## DIAGNOSIS OF UTERINE AND CERVICAL ISTHMIC LESIONS

Hysterography too often is used exclusively for the diagnosis of sterility. We were surprised to find it employed so little in France and in the large gynecological clinics of foreign countries for the diagnosis of tumors in general and of metrorrhagias in particular. How many times does one practice the curettage blindly without knowing exactly what region of the uterus is to be curetted? How many hysterectomies are performed without exact diagnosis because the woman is bleeding near or after menopause?

But it is simple if one utilizes serial pictures to localize perfectly every neoformation in the uterine cavity. It may not always appear on the filling films.

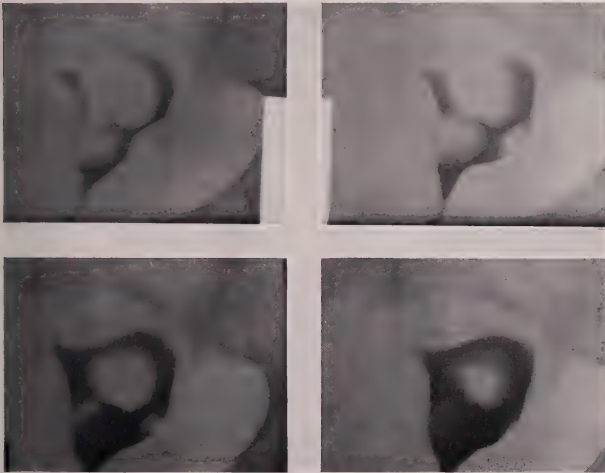


FIG. 3. Hysterogram. In the course of evacuations several submucous fibroid nodules came into view.

In fact, the filling starts generally at the fundus uterine. If one does not carefully study this filling at fluoroscopy, the picture too often shows just a cavity dilated by lipiodol, of which there are no further details. On the other hand, in evacuation pictures taken serially, we will see many details. The submucous and sometimes intramural myoma may show a well defined round and regular ring. The polyp will show up perfectly and if it is pedunculated its position will vary in the course of uterine evacuation. The neoplastic bud will show up distinctly with its indentations which retain lipiodol and that is why we insist upon the necessity of using heavy lipiodol and even on its employment in the study as we have shown with Ledoux-Lebard and J. Garcia-Calderon.



FIG. 4. Hysteroscopic, revealing pedunculated polyp of the lower third of the uterus coming down during the evacuation and forming a valve.

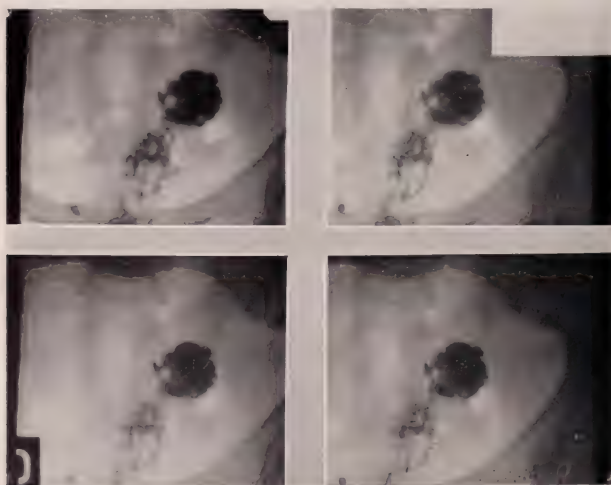


FIG. 5. Hysteroscopic, in a case of epithelioma of the uterus, verified at operation.

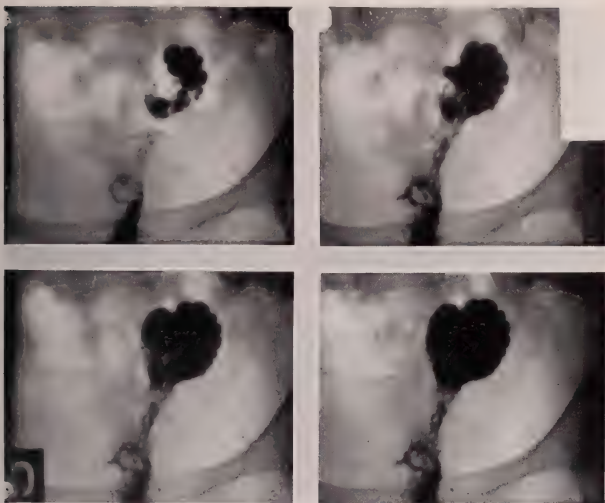


FIG. 6. Hysterosgram, in a case of epithelioma of the body of the uterus, verified at operation.



FIG. 7. Hysterosgram, showing irregularities of the entire uterine mucosa hyperestrogenism (hyperfollicularism), menopause 2 months later.

In this case it is equally important to take evacuation pictures in three-fourths oblique position when irregularity of the mucosa will show up. While the gastroenterologist studies the folds of the mucous membranes, we do not study coarser details yet because of a badly applied technique. Finally, there is much discussion about the aspects of the cervico-isthmic cavity. We know that most of the cancers of the cervix have an endocervical origin. It is important to be particularly attentive and to study carefully the evacuation of this portion. The serial pictures will permit us to differentiate easily the pedunculated polyp in the form of a bell from a fixed irregularity on which biopsy may be performed.



FIG. 8. Hystero-gram, in a case of intracervical carcinoma with metrorrhagia.

#### SUMMARY

I do not want to come back to the advantages of hystero-gram over the blind curettage, advantages which we have emphasized for almost 20 years. I want to show that, thanks to this method, we are able to exactly locate the lesion and in a high percentage to make a diagnosis without having to resort to the curettage or to laboratory examinations. In fact, in the course of uterine evacuation one sees pictures which could have passed unnoticed during uterine filling. We should not forget that the uterine cavity is an actual one, that the lipiodol is very opaque and if the injection is done too rapidly details may escape us. All these details reappear in the course of evacuation with particular clearness. The lipiodol will outline polyps or submucous myomas; it will re-



main between the buds of an epithelioma. It will mark the fine border of a simply hypertrophied mucosa. It will persist in a dilated salpinx. It will show up the irregularity of the cervico-isthmie portion. And even if it is not diagnostic (most often it is diagnostic) it will mark with a perfect precision the exact point on which one must make the exploration or the curettage.

#### RESULTS

It is not sufficient to state facts. We have to add the proof of experimentation, i. e., the clinical results of a method. We have published elsewhere the results in a study of sterility and we will not come back to this study, but it seems to us useful to refer to the study of metrorrhagias by hystero-salpingography practiced according to this method and give the results. We derived them from the thesis of our pupil and friend, Roger Akin, who studied a thousand of our histories and used in his thesis 131 observations of metrorrhagias. Since this time our observations have been considerably enlarged for we resort more and more to hystero-graphy as a diagnostic measure. We prefer, however, in most cases of sterility to resort at first to kymographic insufflation (Rubin test).

The conditions under which we were laboring since 1939 did not permit us to study our last observations with the same exactness as those studied and published in 1937 by Akin. He included only those cases followed from one to ten years and carefully followed up. Two groups of patients have been studied before and after menopause. We can only summarize the results and refer the reader to Akin's paper. Of 85 cases of metrorrhagia premenopausal we found 52 surgical lesions (61 per cent) of which 7 were cancers of the corpus uteri and 33 (39 per cent) metrorrhagias of medical or functional cause. Forty-six cases postmenopausal showed 21 (46 per cent) malignant lesions and 25 (54 per cent) benign lesions. In 19 cases total hysterectomy was performed only on the basis of hystero-graphy and the histologic examination in these cases has confirmed the radiographic test. Only in one case we had to resort to a curettage and biopsy directed on the suspected point. In this series of 131 observations of which some go back as far as 1927 we found 97 correct diagnoses which did not need any other means or confirmation for treatment. Thirty-one cases necessitated a directed curettage, two doubtful cases and one error (a hydatidiform mole, the radiological picture of which was unknown at that time).

These results, more eloquent than all writings, show the value of a technique which is too much neglected by gynecologists because they do not wish to employ a method of vigorous observation.

## CERVICAL PREGNANCY

DANIEL DOUGAL, M.D.

(*Manchester, England*)

As Rubin was one of the first gynecologists to write on cervical pregnancy it is fitting that a communication on that subject should find a place in the Anniversary Volume published in his honor.

His paper (1) appeared in 1911 and was divided into four parts:

1. Report of a case admitted to the service of Charles Goodman in 1910.
2. Anatomical criteria which determine the cervical form of placenta previa.
3. A discussion of the clinical features of cervical pregnancy.
4. A survey of the literature.

From Goodman's private records, quoted by the author, it appears that the case was diagnosed as a ruptured ectopic pregnancy with diffuse intraperitoneal hemorrhage. From the third month of her third pregnancy and usually following coitus, the patient had repeated attacks of acute abdominal pain and finally, during the fifth month, a more severe attack terminating in a fainting spell. She was operated upon as an acute abdominal emergency when it was found that the distended and thinned lower part of the uterus had ruptured anteriorly close to the left broad ligament. A further rupture occurred during the course of the operation and was accompanied by the escape of liquor amnii and protrusion of a fetal limb. The fetus, of about five months' development, was extracted through the tear and the uterus then removed by subtotal hysterectomy. On cutting across the cervix it was noticed that there was considerable placental attachment below the level of the incision. The patient recovered.

The specimens removed were examined by Rubin and are fully described and illustrated in the paper. Among his microscopic findings were the following:

Some decidual tissue was present in the upper part of the uterus but no chorionic villi above the level of the internal os and isthmus.

Cervical glands were recognizable opposite the placental attachment.

Numerous giant trophoblast cells had deeply invaded the cervical tissue, even extending to its outermost limits.

After briefly outlining the different views about the origin and anatomical characters of the isthmus and lower uterine segment, Rubin expressed the view that the isthmus is really an arbitrary segment of the uterus without definite anatomical limitations. The most positive statement that could be made about it was that it is situated in the immediate vicinity of the internal os, is the most constricted portion of the uterus and that a line joining the points of entry of the uterine vessels on each side corresponds approximately to the internal os and isthmus. From this it would appear that Rubin did not at that time consider it necessary to distinguish between "isthmial" and "cervical" pregnancies. As regards the cervix, he pointed out that although the decidual reaction is imperfect in that situation, nidation might yet take place as it does in the case of the

Fallopian tube or ovary, but he then went on to say that "the cervical form of placenta previa need not necessarily arise from the circumstance of an ovum primarily taking root in the cervical mucosa." Evidently Rubin did not attach much importance to primary cervical nidation in the etiology of cervical pregnancy but believed that in most cases the ovum is initially imbedded close to but above the internal os and afterwards penetrates the tissues of the cervix. His use of the term "cervical placenta previa" further bears this out as a placenta previa is one that lies ahead (of the ovum) or leads the way, which need not necessarily be the case in true cervical pregnancy.

Discussing the liability to spontaneous rupture of the uterus when the placenta is implanted on the cervix, Rubin mentioned three etiological factors—inadequate resistance to syncytial invasion, increase in intracervical tension and the cramping effect of the confining walls of the true pelvis.

In his review of the literature, he gave short abstracts of eight cases but with one exception, that reported by Jaschke, they appear to be examples of placenta previa in which a portion of the placenta had extended on to the cervix. Goodman's and Jaschke's cases are very similar and in both of them the ovum appears to have been implanted close to the isthmus if not actually on the cervix.

Summing up Rubin's views on cervical pregnancy as revealed by his 1911 paper, it may be said that he then regarded the complication as a variety of placenta previa in which the placenta was partially attached to the cervix and the remainder of the ovum usually occupied the body of the uterus to a greater or less extent.

A recent (1945) paper by W. E. Studdiford (2), modestly described as "a partial review of the literature and a report of two probable cases," has brought the subject up to date. Studdiford defines cervical pregnancy as one in which nidation and subsequent development of the ovum take place in the cervix and the body of the uterus remains uninvolved. He thus excludes cases of isthmico-cervical pregnancy in which a placenta previa is partly attached to the cervix but the ovum develops in the uterus. Details are given of 28 cases of cervical pregnancy as so defined, including those reported by Goodman and Jaschke, but in only half the cases was there pathological as distinct from clinical evidence to support the diagnosis. Of the two "probable" cases reported by Studdiford himself, the second is of special interest as the gestation sac appears to have ruptured into the vaginal fornix through the right posterolateral wall of the cervix.

After sifting the available evidence, Studdiford concludes that true cervical pregnancy is a possibility and may be regarded as a variety of ectopic pregnancy. This is obviously a great advance on the older view that cervical pregnancy is a form of placenta previa.

The terminations of cervical pregnancy are similar to those of other ectopic gestations, premature interruption being the rule because of the unfavorable environment.

The ovum may be expelled through the external os as an abortion, possibly at such an early stage that it escapes recognition, or the process may be threatened or incomplete.

The distended cervix may rupture into the vagina, the pelvic cellular tissues or the posterior cul-de-sac.

The ovum may grow upwards into the lower or even the upper segment of the uterus and the pregnancy continue for a further period or even to term. As it is now accepted that the lower uterine segment is differentiated during the early months of pregnancy it seems likely that this part of the uterus was involved in Goodman's case and that it was the lower segment rather than the cervix which ruptured.

Finally, the pregnancy may continue to term within the cervix. This is very exceptional but occurred in Tarnier's case (1887), mentioned by Studdiford.



FIG. 1. Mesial surface of right half of uterus after sagittal section

The patient had a cervical fibroid which obstructed labor and necessitated delivery by cesarean section. She died shortly after the operation and at autopsy the distended thin cervix was found to contain both fibroid and placental site and to have the small uninvolved corpus perched on top of it.

Cervical pregnancy is usually associated with severe and even dangerous hemorrhage but in the following case which occurred in the present author's practice the bleeding was only of moderate amount.

#### CASE REPORT

Mrs. M., aged 39 years, sought advice in April 1939, for a hemorrhagic vaginal discharge of eight weeks' duration. Menstruation was regular, 5 28, and she had not missed any periods since her last pregnancy. Bleeding commenced on the expected date of the February period and continued up to the time of her operation two months later. There had been two other pregnancies, the last one eight years previously and complicated by ante-partum hemorrhage in the 39th week. On examination, the patient's general health was found to be good and she did not appear to have lost much blood. There was a profuse vaginal discharge, hemorrhagic and extremely offensive. On palpation, the cervix was

found to be the seat of a friable "proliferative" growth which bled freely during the examination. The body of the uterus was of normal size, firm and in an anteverted position. Carcinoma of the vaginal cervix, stage I, was diagnosed and the patient admitted to hospital for a Wertheim operation.

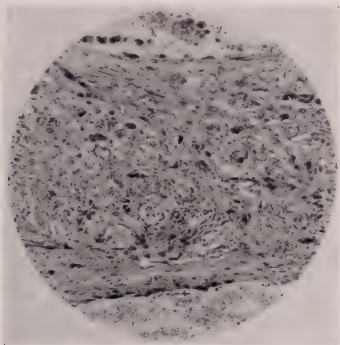


FIG. 2. Large trophoblast cells invading fibromuscular tissue and blood vessels of the cervix

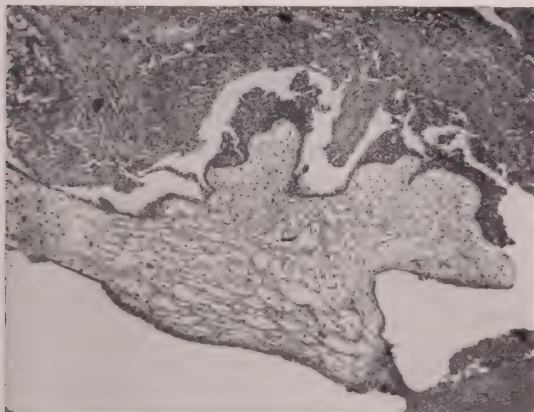


FIG. 3. A large chorionic villus

At this point it must be confessed that the clinical history and findings on palpation were so typical of cervical carcinoma that neither a speculum examination nor a biopsy was included in the preliminary investigation. Indeed, it was not until the cervix was inspected at the conclusion of the operation that any doubt arose as to the correctness of the diagnosis. Fortunately, the patient made an uninterrupted recovery and was alive and well six years



later. It has not been possible to trace her since the recent war as her home was destroyed during the enemy bombing attacks of 1940/41.

The specimens examined were removed by Wertheim's operation and consisted of the uterus, both uterine appendages and a number of lymphatic glands.

*Uterus.* The uterus measured 8 cm. in length, 5 cm. in width at the level of the fundus and 3.5 cm. anteroposteriorly.

On sagittal section (fig. 1), the macroscopic appearances of the corpus and isthmus were normal but in the cervix there was a dark red or black mass of tissue attached mainly to the anterior and left lateral aspects of the cervical canal and protruding between the separated

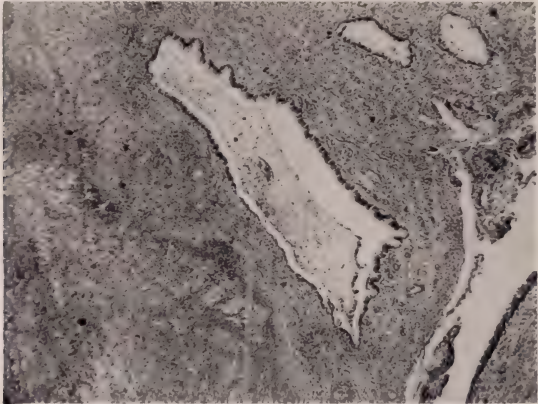


FIG. 4. Cervical glands in close proximity to molar tissue (below and to left)

and somewhat thinned out anterior and posterior lips. The mass was friable, necrotic and grossly infected. The microscopic appearances were as follows (figs. 2, 3, 4):

*Corpus and isthmus.* There was no muscular hypertrophy. The endometrium was in the secretory phase without decidual reaction or trophoblastic invasion.

*Cervix.* The histology was normal except beneath the attached mass where vascular engorgement, hemorrhage, fibrinous deposits, leucocytic infiltration and invasion by large trophoblastic cells were prominent features. Scattered decidual cells were also present. The mass itself had the typical structure of a blood mole and here and there chorionic villi were still in organic union with the cervical tissues. Cervical glands were present in close proximity.

*Appendages.* The uterine appendages were normal and there was a large corpus luteum of pregnancy in the left ovary.

*Lymphatic glands.* The lymphatic glands showed evidence of infection.

#### DISCUSSION

The case is submitted as one of cervical pregnancy but it is necessary to consider two possible alternative diagnoses, incomplete corporeal abortion with dislocation or implantation of chorionic tissue and chorionepithelioma.

A portion of placenta adherent in the uterine cavity may be so displaced during

the process of expulsion that its attachment appears to have become cervical. Further, Parker (3) has described a case in which a fragment of placental tissue became grafted in a cervical laceration during labor and having acquired a fresh blood supply survived for nearly a year.

These two possibilities can be ruled out in the present case as the pregnancy was obviously of recent date and very early, to judge from the menstrual history and appearance of the corpus luteum, and terminated without leaving any evidence of its having been present in any other part of the uterus but the cervix. The other possibility, chorionepithelioma, is not supported by any histological evidence, all the appearances being consistent with a diagnosis of retained products of conception following (cervical) abortion.

The distortion of structures which occurred in this case makes morphological reconstruction difficult but it is suggested that the gestation sac developed in the wall of the upper part of the cervix, that hemorrhage into and around it then occurred from imperfect decidualisation and that the resulting blood mole then protruded and finally ruptured into the cervical canal from which it was incompletely expelled. If this is the correct interpretation, the similarity to tubal abortion, the most frequent termination of tubal pregnancy, is evident and lends support to the view that true cervical pregnancy is not a variety of placenta previa but of ectopic gestation.

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## DIAGNOSIS AND THERAPY IN UNUSUAL CASES OF HYPOTHYROID DYSCRASIA IN GYNECOLOGY AND OBSTETRICS

J. R. GOODALL, M.D.

(*Montreal, Quebec*)

Thyroid dyscrasias of the deficiency type outnumber the excessive secretory cases in the ratio of about 50 cases to 1 in private practice. This article will deal chiefly with the unusual, but very common, clinical types of hypothyroidism. Stress will be laid upon the unusual characters of the symptoms and signs—a recognition of which will lead to appropriate treatment and prompt improvement of the distresses.

To facilitate description, the first part of the paper will deal with the unusual cases in gynecology; the second part with the obstetrical cases.

### GYNECOLOGICAL CASES

Starting from the head and working downwards, we first encounter headaches. These fall chiefly into two groups: severe headaches of a local or general nature; and the migraine type of local pain. These two may prove to be ultimately of the same nature. The common description given by the patient in the first group is that the headache frequently begins in the back of the neck and movement of the head causes exacerbation of the pain and a creaking in the cervical vertebrae simulating arthritis. This description is so characteristic as to be diagnostic of neuritis. By careful study of these and similar symptoms in other parts of a woman's body, I have come to the conclusion that deficiency neuritis and arthritis are in many cases clinically indistinguishable. The headaches may spread or localize over the mastoid or temple or supra-orbital region. It frequently passes off as the day advances.

A second characteristic deficiency type is that which is experienced only at menstruation, or greatly increased at that time. Its location is various, but is generally relieved when the menses is properly established.

In the migraine type the pain is localized over a limited area. When an extensive area is involved it may become a hemicrania. A careful history in these cases is of the utmost importance for individual and familial traces of allergy manifested in the protean symptomatology of allergic diseases. These cases, if subject to careful analysis, show in a large percentage a thyroid deficiency and a complete absence or partial deficiency of the normal gastric acidity. When both these findings are present, the administration of normal amounts of these two products will usually result in a complete disappearance of distress.

The next type of cases concerns the intrathoracic organs. About five years ago I was called in consultation to see a patient recently delivered, after eclamptic convulsion, of a dead child. She had developed sudden attacks of severe retrosternal pressure and constricting pains with inability to retain any food. Vomit-

ing was almost immediate after ingestion. Nothing was found on physical examination or by x-ray to clarify the situation. This went on for several days without improvement, and her general state of health became very grave. I had not suspected thyroid dyscrasia, but on careful examination it was found that she was allergic to several things when in good health. Her weakened state post partum, aggravated by the toxemia, had increased her susceptibility. When given thyroid she promptly recovered, digested her food and began to gain in weight. She has had three recurrences when she stopped the therapy. On examination of the stomach contents there was no free hydrochloric acid and the addition of small doses of the acid made her restoration more rapid. She has to continue this medication steadily or her symptoms recur. She has had two normal deliveries since I first saw her. Since this case, eight others of a similar, but less pronounced, type have come under observation so that now the syndrome is easily recognized and prompt relief is obtained either by thyroid alone or by the combination of thyroid and hydrochloric acid. Most of these cases had been treated as cardiac cases before the diagnosis was made.

There is another series of cases which I have classified as pseudo-anginal. The first of these was a member of my family. She had complained for a long time of chest pain and dyspnea on exertion. She had gone to a cardiologist who, on reading her cardiogram, had told her that her heart was not quite normal. This could not have been right, because when on pleasure bent there was no limit to her capacity for activity without any distress whatsoever. However, emotional upsets frequently precipitated the attacks. These were extremely distressing: she would become rigid, gasping and in acute chest pain; the chest felt as though it were in a vise; but her color would not change nor the pulse vary. In spite of medication these attacks persisted. I was called in consultation and finding a family history of allergy and definite signs of deficient thyroid secretion, gave her thyroid therapy and the attacks ceased. It is now five years since the treatment was started and she has had only two attacks in that time usually when the thyroid therapy was interrupted.

Since then many similar cases have come under observation with equally happy results. Recently one of my colleagues had a somewhat similar case. He believed her to be obviously a cardiac patient so he referred her to a specialist. After six weeks of treatment by the cardiologist there was no improvement. I advised him to look into her thyroid activity. Her basal metabolic rate was minus 18 and when placed on treatment the symptoms promptly disappeared without recurrence. Later, on questioning, it was found that there was a distinct familial allergic tendency.

Several years ago I was called in consultation to see a young girl of 21 years who had been under treatment by two lung specialists for a chronic bronchitis. She had been confined to bed for the past three months for an uncontrollable cough. She had undergone numerous examinations and many x-ray plates had been taken. Her sputum had been examined and a vaccine made and a series of injections given without any appreciable improvement. The spasms of coughing were so severe that uterine bleeding set in. During my visit, a spasm of coughing

came on with dyspnea and with all the signs of sudden asthmatic attack. Careful examination revealed signs of a multiple endocrine dystrophy, and a family history of allergy. I recommended thyroid therapy. A prompt cure followed and the uterine bleeding ceased promptly. Several other spastic cases of a similar nature have since come under observation and have responded promptly to treatment.

Probably the most interesting cases are those of spasm of muscular structures in the vicinity of the gallbladder. These cases are numerous and they run a definite course. Let me outline one of the earliest. A doctor's wife had repeated attacks of what was diagnosed as biliary calculus. These were severe and became more and more frequent. She was a graduate nurse and could describe her symptoms very accurately. They were indistinguishable from those of calculus. X-ray revealed no calculi, but the gallbladder filled and emptied very slowly. Finally a normal gallbladder was removed, but the attacks went on as before. Later she came under my care for a pelvic condition. There were very marked signs of thyroid dystrophy, and a gastric examination showed an absence of free hydrochloric acid. The administration of these two medicaments was followed by a complete cessation of the attacks. The patient resented the need of taking these remedies for the greater part of her life and tried the effect of stopping them. The attacks, after an interval, returned with great severity. The vomiting in this and other similar cases is very severe and almost projectile in character, and the patient gets no appreciable relief from huge doses of morphine, but atropine or amyl nitrite will usually give prompt relief. Another patient was operated upon by me for a pelvic tumor. Three days after the operation she had a violent attack of pain in the right upper quadrant, simulating gallstones. I knew it could not be that, because I had examined the gall-bladder at operation and had emptied it with ease. The attack passed off with the application of heat. Two weeks later when on a week end trip she had a much worse and more violent attack with inability to retain anything. She was brought home and the pain gradually wore off. I elicited the history of similar milder attacks spread over a period of years, but that in her weakened state since the operation the attacks were intolerably severe. She gave the history of occasionally breaking out with hives before or after the attacks. There were definite signs of deficiency in thyroid and a gastric analysis revealed achlorhydria. I assured her that she could go away the next weekend without fear of a recurrence. She is a difficult patient to control in her indulgences and omissions, so that occasional attacks come on as a consequence. However she knows that these follow upon her lack of care.

Many similar cases have come under observation. In these, a careful history taken with a view of eliciting any personal or familial allergy is of the greatest aid, together with an almost total absence of the usual gall bladder pain which is referred to the right scapular region. It is impossible, in the present state of our knowledge, to determine the cause of these symptoms. They have all the hallmarks of a muscular spasm. Whether of gall-bladder or pylorus it is impossible to determine. In only one of such cases did jaundice follow one of the many attacks. The late Dr. Edward Archibald, to whom I had related several



of these cases, had had similar cases which revealed nothing at operation and removal of the gall-bladder did not relieve the attacks.

*Colitis.* Colitis is one of the most common of women's diseases. It constitutes about 5 per cent of my office practice and I am convinced that a very large percentage of cases of operations done for appendicitis and ovarian trouble are really colitic cases with fixed pain. The cases of colitis affecting the whole of the colon, or cases of shifting pain along different parts of the colon at different times, lend themselves easily to diagnosis, but on the other hand, cases of fixed pain localized in any of the abdominal quadrants may tax the acumen of the most careful diagnostician. Many of the cases of colitis are due to allergy, but many, if not all, have a nervous element as well. In many of the allergic ones there is an absence of hydrochloric acid in the stomach secretion, and where this is the case and there is achlorhydria, the treatment is usually followed by most gratifying results. Naturally when the nervous element is predominantly large, crises of nervous tension, operations and domestic strife determine the frequency and severity of the attacks. A careful case history is the *sine qua non* for a rational diagnosis and treatment. It has been my experience that a quiet explanation of the nature of the case to the patient will nearly always gain her cooperation and understanding and help her to cultivate equanimity and avoid pitfalls. The continuance of the high nervous tension militates greatly against a speedy recovery. Moreover, many of these patients, with their abdominal pain and associated backache, are seldom able to appraise their condition properly, so that they fear that they are suffering from some grave incurable condition, such as cancer or some other progressive disease. X-ray and analysis seldom leave the matter long in doubt.

*Pituitary thyroid dyscrasias.* It is in this field that one meets with the most striking responses to therapy in gynecology. It is a general rule, not without its exceptions, that cases of athyrea are disposed to menorrhagia or metrorrhagia, and that hypothyroidism is prone to produce scanty menstruation or amenorrhea. One of the common types is that of a young girl in the first years of puberty and complaining of menorrhagia or metrorrhagia. In many of the cases the thyroid has been enlarged since the onset of the menstrual periods. There are often signs of a generalized gland deficiency, involving chiefly the anterior pituitary gland. There is frequently in addition to the enlarged thyroid, hirsutism, a high palate, milk spots on the nails and teeth, dry hair and skin and other signs of thyroid dyscrasia. The case would seem hopeless from the point of view of therapy, and I must confess that anterior pituitary extracts have proven quite ineffective in such cases, but that one can accomplish extraordinary results with exhibition of thyroid.

*Dysmenorrhea.* In many cases of uterine crampy dysmenorrhea occurring during the first day of the menstrual flow, the cause can be laid to uterine allergy. There are many other causes of course, but in private practice allergy will account for about 20 per cent of the cases. The high palate, and the other signs of thyroid deficiency, may or may not be present. If present, the diagnosis becomes easy, but if absent in such cases, it will repay the trouble of using the therapeutic test by giving the patient small doses of thyroid while she is kept under close

observation, and increasing the dose carefully until relief or cardiac acceleration occurs. Many of these cases are promptly relieved and it is common to have the patient state that her first menstruation after treatment came on without symptoms. Many of the cases are associated with a degree of anemia, and the exhibition of iron under these circumstances is highly recommended.

In many cases of vaginal thrush and of trichomoniasis, treatment will bring prompt results but leave the vagina a beefy reddish color with a dry glossy surface and with this residue the disease promptly returns when treatment is stopped. In a good percentage of these cases the tissues return quickly to the normal state under thyroid therapy. It is reasonable to assume that, as absence of thyroid causes dryness of the skin, the vagina, being a squamous surface, may be similarly devitalized and disturbed in its normal functions.

In cases of pruritis vulvae, especially in those showing an eczematous, dry or moist, condition of the vulva and cervical tissues, in the absence of glycemia, it is advisable to test out the thyroid efficiency and to examine for the existence of achlorhydria. If these defects are present the great majority of the cases respond promptly to treatment by thyroid and hydrochloric acid, and a soothing application to the affected parts. Three months ago a patient with one of the most acute cases of vulvitis and vaginitis came to me after unsuccessful treatment by one of my confrères. The discharges were negative to trichomonads or other recognizable bacteria. The usual treatment by desiccating antiseptic powders had no appreciable effect in relieving the distress which was reducing the patient in health and mental stability. Then it suddenly dawned upon me that there might be an allergic state. Enquiry elicited an allergic history and lately just before the onset, a severe mental shock. The patient was then put on thyroid and small doses of hydrochloric acid and the relief was prompt and complete.

There is another condition that has caused not a small amount of speculation as to its origin. This is a cervical disease in which there is a profuse watery leucorrhea, and on examination the cervical os is patulous, moist with a copious flow of clear secretion, and the margins of the os and portio present an edematous glazed appearance. These cases are very numerous and intractable to cautery. When healing of the cauterized structures is completed the cervix shows little improvement, if any, over its precautery state. The condition was very baffling until it was found that this is an exudative allergic state. In a few of these cases, associated with fibroids of the uterus, hysterectomy was performed, and on opening the uterus the majority of them presented an advanced state of uterine edema, indicative of an allergic state of the mucosa and thereby explaining the copious watery discharge characteristic of this disease. The appropriate treatment of the condition for the cure of allergy gave excellent results in the majority of cases, especially when the thyroid deficiency was associated with an achlorhydria.

#### THYROID DYSCRASIAS IN OBSTETRICS

Dystrophies in the field of obstetrics offer a wide and very diversified field of symptoms and signs. Probably the most interesting are the troubles leading to *sterility*.

It is now established beyond doubt that a very large percentage of cases of sterility, both in the female and the male, owe their source of trouble to a deficiency in thyroid secretion. When it has been established by examination that the female passages are patulous and that the sperms are in a sufficiency and of normal activity, whether or not the woman presents clinical signs of insufficiency of the thyroid, a small dose of thyroid very frequently brings a prompt improvement in fecundity of the individual. Genito-urinary specialists affirm that the same holds true for the male. Many women now know that they can remain sterile as long as they wish and become pregnant also when they wish through the use of thyroid. Thyroid has become a routine in all cases of this type and the results have been most gratifying. But the happiness experienced by the conception is often destroyed by miscarriages in these cases, because the thyroid tablets are often withdrawn once conception has taken place. It is imperative that the dose of thyroid be continued throughout the pregnancy in increased doses, or a faulty implantation and hemorrhage may destroy the pregnancy. This leads us to the subject of thyroid in abortion. Thyroid deficiency is one of the common causes of this disease, and the exhibition of thyroid in the early state of the uterine pain and bleeding will frequently permit the pregnancy to continue to term if damage of an irreparable nature has not preceded the symptoms of abortion. It is a peculiar paradox that in so many cases of thyroid deficiency a large number are sterile owing to the insufficiency, whereas in others fertility seems not to be interfered with, but habitual abortion is the rule.

It is difficult, in fact impossible, to explain the action of thyroid in these cases. Does thyroid merely heighten general cell activity, or has it some specific action? There seems no adequate explanation for the lack of fertility in hypothyroidism other than that of lowered cell vitality. But beyond this may be some deep intraovular or intraspermatic activity for which thyroid is a specific and essential need. But in abortion, the fault would seem to be deep seated, inasmuch as many of these cases show a definitely diseased pregnancy. The pathology that is found varies greatly, but the variations are probably but late sequelae of a primary cause. When painless hemorrhage is the first sign of impending abortion, it may be doubted whether the exhibition of thyroid or the rest brings about arrest of the sign. But if the pregnancy continues there could not have been any gross lesion of the fetal structures. Therefore the hemorrhage might be classified as incidental. But in most of these cases of completed abortion, one finds that the fetal structures are gravely diseased. There are numerous cases where the sac comes away intact and the fetus has been completely digested, the French call this a "white egg." In this type there seems to be an underdevelopment of the placenta and membranes. In another type hemorrhage may fill the sac and no sign of fetus can be detected on careful search. Many other subchronic hemorrhages may be present, resembling spurious fetal sacs. In all these cases if signs of thyroid deficiency exist, one can assure one's patient that the next pregnancy will be successful if she is careful to carry out the prescribed treatment of thyroid and rest in the early months of conception.

*Transmission of thyroid defects.* From careful observation it has been my

impression that thyroid instability is definitely transmissible. The mechanism of the transmissibility would seem to be somewhat as follows. Physiologists tell us that the cellular activity of the fetus is about 25 times faster than that of the adult, and that therefore, if thyroid necessity is bound up with cellular activity, the fetus must require a considerably larger amount of thyroid than would the same individual in adult life. In a word, the thyroid sufficiency is in a gradual diminuendo throughout life. I think one cannot dispute that statement. It is in accordance with facts, and rational. Mothers during pregnancy, require a greater elaboration of thyroid, both on account of the baby's needs and on account of the maternal growth of uterus, breasts, heart, in fact, of most organs. This excessive need of thyroid is evidenced by the enlargement of the thyroid in the early months of pregnancy. Greek mothers were in the habit of measuring their daughters' necks at the time of marriage, and any enlargement of the contour after marriage was taken as *prima facie* evidence of early pregnancy. It would seem, therefore, that the growth demand must be met to insure normal development of both mother and fetus. If the mother cannot supply the necessary amount, it is my impression that the fetal thyroid is called into operation before it is due, and the overcharge upon the fetal structures will give rise to fatigue, or worse, exhaustion, and result in a thyroid instability of lesser or greater degree. It is interesting also to contemplate what would be the effect upon the normal fluidity and synchronism of development in the fetus generally, in high degrees of lack of supply of thyroid in the early stages of fetal development. It has been my practice for years to observe closely the thyroid activity in pregnant women, and the use of thyroid in therapeutic doses has produced most gratifying results.

*Subinvolution.* Involution of the uterus is an interesting and intricate process. No one knows what the normal rate of involution is, but one may appreciate by palpation only the grosser forms of the disease. There are all degrees of the imbalance, ranging from the diminutive uterus and infantile vulva of the woman at six weeks after labor, to the uterus still the size of a two month's pregnancy three months after labor. We conceive by experience that a certain rate of descent is normal and that departures from this require interference. In my book on puerperal infections, it was considered that infection was the common cause of subinvolution. Today, in the light of our present knowledge, we must modify that concept. There are other and more frequent causes. It is true that ten years ago puerperal infection was much more common, and perhaps equally true that infection in those days was the most common cause of subinvolution, but today, this is not so frequent a factor. Others of equal potency in retarding involution are hypothyroidism and hyperestrinism. Retarded involution with its prolonged lochia will, in a large percentage of cases, respond quickly to thyroid therapy. In other cases where overactivity of the ovaries seems to be the source of the trouble I know, as yet, no means of neutralizing the overproduction, and the persistence of the causative factor leaves the uterus in a large, soft, subinvolution at first, later, fixation of tissues follows and the end result is the large hard uterus of chronic metritis.

## SYMPTOMS AND SIGNS OF HYPOTHYROIDISM

It has been my clinical experience that the estimation of the basal rate is done so hurriedly and by inexperienced persons that its value is very questionable. Recently, to cap my unsatisfactory experiences, I sent a rather nervous patient to the hospital for a basal rate and the report came back plus 54. I knew this to be wholly wrong and four days later I had the same specialist go to her house and take it again, and the estimate was minus 19. So frequently is a patient worked up to a nervous state by the anticipation of a test of which she has no knowledge, that her rate runs a great deal higher than is her normal. So commonly is the reading too high that I invariably subtract 10 per cent for this excitation, so that a minus 10 becomes a minus 20, and a plus 5 becomes a minus 5. Moreover, there is a profound objection among doctors, and rightly so, to condemn the fixation of two percentages between which a patient's rate is considered normal. Such, for example, that all patients between minus 10 and plus 10 are within normal rates. This has proved so erroneous that many patients well within this ratio have proved beyond any doubt that their symptoms arise out of their thyroid dystrophy. So it has come to pass, owing to this large margin of error, that the therapeutic test is the more accurate and the more satisfactory. To the wary physician, hypothyroidism in both its pronounced and larval states will rarely escape his observation, especially if he is *au fait* concerning the more recent signs of thyroid deficiency. It is not my wish to enumerate the many familiar signs and symptoms of thyroid deficiency, nor do I wish to describe those pronounced cases that are so striking as to be recognized even by the layman. There are certain less well known of the signs which are so commonly distributed about a patient that they seldom escape the physician who is aware of their characters. There is the feel of the skin, the feel of the hair, the high palate, indicative of early developmental pituitary disease, enlarged thyroid, but above all, the most common and certain signs, "milk-spots" on the finger nails and less commonly on the teeth, and a deeper than normal separation of the nail from its matrix at the free margin of the nail. These are the commonest of all the signs of hypothyroidism, and are among the most accurate. The reason for these "milk-spots" is to be found in a defective nutrition of the nail and teeth matrix. It is commonly known that the integumentary surfaces are prone to show the defects of thyroid deficiency. Witness the myoedema, the dry thick skin, the dry hair, and it is easy to understand why the nails and teeth suffer in their nutrition and show the defects described above. The nails and teeth are but appendages of the skin.

In a large percentage of cases of thyroid deficiency there is also a defective acid formation in the stomach. What the connection is I have never been able to explain, but the coincidence is extremely common, so that an interdependence must exist. When there is a degree of achlorhydria or complete absence of hydrochloric acid, then the element of allergy is frequently present to obscure or accentuate the symptoms of hypothyroidism. In 1939, at the state medical meeting at Grand Rapids, I emphasized the importance of allergic states in associ-



ation with hypothyroidism and achlorhydria, and outlined the remarkably astounding improvement by supplying these deficiencies.

In gynecological and obstetrical conditions, allergic manifestations are even more common than in other spheres of medicine. These states manifest themselves in one of two ways, either as exudates or as spasms. There is no part of the body that is immune to these allergic symptoms. They explain the remarkable prevalence of spasms simulating gallstones, renal colic, intestinal, uterine and skeletal torture, and the exudative types are equally common as local edemas, eczemas, pruritis and hemorrhages—most of which respond remarkably to combined treatment with hydrochloric acid and thyroid. In the same paper, mentioned above, I related the histories of 20 cases of major heartburn in the last trimester of pregnancy, in which a gastric analysis was done. In 18 of these there was complete achlorhydria and the heartburn was due to diacetic or butyric acids—products of fermentation. Sodium bicarbonate is the customary remedy taken by women, but one should understand that this remedy can give but temporary relief, whereas small doses of hydrochloric acid give prompt and continued comfort, if taken as prescribed. The addition of a small dose of thyroid greatly increases the efficacy of the treatment.

The method of administration is purely empirical. The therapeutic test is the essence of its employment. The thyroid preparation that was almost always used was that of Burroughs, Wellcome because the dosage of the tabloids is better graded for therapeutic tests. Usually one begins with  $\frac{1}{16}$  of a grain of the desiccated gland t.i.d. The patient is examined after a week and if improvement has followed and the pulse is unchanged the dose is increased to  $\frac{1}{8}$  t.i.d., and so on each week, until the symptoms have disappeared or the pulse begins to show saturation. If the hydrochloric acid is required in allergic states, the dilute preparation is prescribed in doses of two to five drops after each meal, in a half glassful of water. It is extraordinary what small doses are required to produce results. Occasionally in severe allergic states the dose must be increased to 10 drops, but very seldom beyond that quantity.

## UTERO-TUBAL INSUFFLATION IN UTERINE MALFORMATIONS

O. JURGENS, M.D.

(Buenos Aires, Argentina)

The graphic representation of the phenomena produced during the utero-tubal insufflation, introduced by Rubin and demonstrated by his apparatus, has given this method of investigation a scientific basis.

The information derived from its application to the determination of utero-tubal permeability is manifold. The characteristic curves of the normal tubal conditions with perfect gas transit and normal contractility, as well as the conditions of the utero-tubal spasm, the partial or total occlusion of the tubes, are well known.

Even though insufflation has probably been performed in cases of genital malformations, I have not been able to find any references on this subject. For this reason we present our experience in this field.

### CASE REPORTS

*Case 1. History.* (#3439) Z. G., 32 years old, married, complained of having spontaneous abortions. Though all methods of therapy were used, she could never carry to term.

*Examination.* Normal vulva and vagina; cervix of nullipara with many cysts; uterus slightly in retroflexion, somewhat increased in volume transversally; hysterometry—8.5 cm.; normal adnexal.

A uterine malformation was suspected.

*Course.* Hysterosalpingography was performed (fig. 1A). Uterus bicornis unicollis, somewhat deviated to the right, was diagnosed.

The patient became pregnant again, with probable nidation in the right horn. The pregnancy continued to full term but because of functional dyskinesia, probably related to the malformation, an abdominal cesarean had to be performed. The fetus was alive. The insufflation performed subsequently was frankly positive at a pressure of 80 mm. Hg. (chart I). Auscultatively there was an evident transit of gas. The characteristic phrenic pain was present in both shoulders.

*Case 2. History.* (#3754) A. I., 26 years old, single, complained of having premenstrual dysmenorrhea. She could not remain in an erect position because of the intensity of her pains. She had menstrual delays of eight to ten days and bleeding periods varying from eight to nine days, three of which were profuse.

*Examination.* Normal vulva; double and totally septate vagina with double uterine cervix; uterus increased in volume, in antelexion, presenting a small depression on the bottom; normal adnexal.

*Course.* Hysterosalpingography revealed the existence of a double uterus with permeable tubes and contrast substance within the abdominal cavity (fig. 1B). The insufflation (chart I) was frankly positive at a pressure of 75 to 80 mm. Hg. with positive auscultative and pain manifestations.

*Case 3. History.* S. H. (from the Cons. Externo del Hosp. Durand Obstetric Clinic of Professor Boero) complained of sterility.

*Examination.* Uterus increased in volume transversally, in antelexion, mobility limited; normal cervix.

*Course.* The hysterosalpingography (fig. 1C) revealed a double uterus with ascending and narrowed left tube. The insufflation (chart I) was demonstrative of a partial occlusion.



FIG. 1. A. Case 1. B. Case 2. C. Case 3.

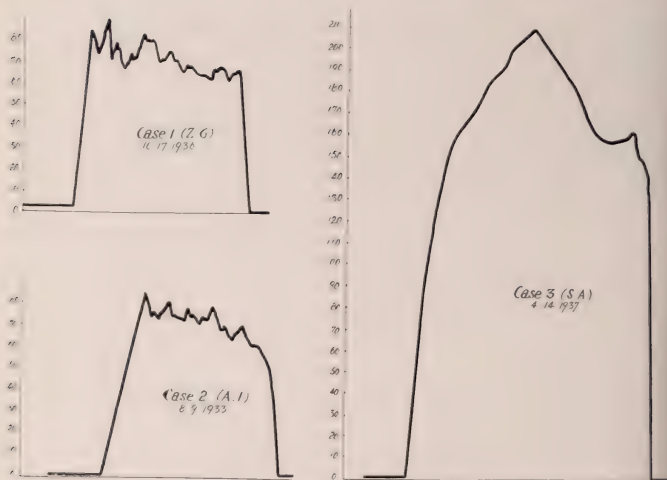


CHART I

Highest pressure was 210 mm. Hg. with slight fall in a smooth curve. The patient felt pain in her left iliac fossa.

*Case 4. History.* (#24625) (From the Obstetric Clinic of Professor Boero). The patient has had repeated abortions; one full-term pregnancy, fetus with congenital debility died one month after birth; and another full-term pregnancy, fetus alive. She complained of post-abortion hemorrhages caused by incomplete abortions.

*Course.* The diagnosis of an uterus duplex unicollis was made before this admission by insufflation. This was confirmed by operation during which the right uterus was removed. The hysterosalpingography (fig. 2A), pre-operatively, revealed a double uterus, the left more developed than the right and containing the products of pregnancy just before aborting. The second radiograph (fig. 2B) taken some months after the hysterectomy showed the remaining uterus with its tube. The insufflation revealed permeability with the highest pressure of 80 mm. Hg. (chart II). Auscultation and shoulder pain were positive.

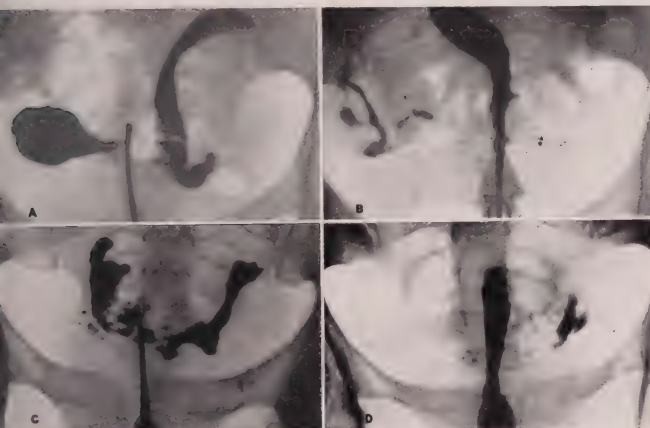


FIG. 2. A. Case 4, pre-operative. B. Case 4, post-operative. C. Case 5. D. Case 6.

*Case 5. History.* (#4719) S. T. complained of amenorrhea of three months duration.

*Examination.* Normal vulva; septate vagina; double cervix (the right smaller), in both there were signs of softening and coloration of pregnancy. Palpation disclosed the existence of an uterine tumor somewhat to the left side and globular, corresponding to the size of a three months pregnancy. On the right side, attached to the uterus, was a small mass of firmer consistency. This gave the impression of a hypoplastic hemiuterus.

*Course.* The hysterosalpingography (fig. 2C) (#17585) of the Radiologic Service of the Hospital Aleman, taken before the evacuation of the uterus disclosed a larger cavity without showing the right hemiuterus. The hysterosalpingography in that case revealed an initial spasm which was overcome at a pressure of 210 mm. Hg. at which time a sudden sharp drop in pressure denoted the passage of gas through the tube. This was seen on the graph by a descending curve (chart II). Pain in the shoulders and auscultation were positive.

*Case 6. History.* (#4919) M. T., 26 years old, complained of an amenorrhea of four months duration. She also had the sensation that something was protruding from the vagina.

*Examination.* Normal vulva; septate vagina with evident maldeveloped left vagina. No cervix could be seen in the right vagina. In the left vagina, the cervix was somewhat

hyperplastic and Hegar sign was positive. Bluish discoloration and softening were also present. Uterus was in ante flexion and globular, corresponding to a pregnancy of four months. On the right a small sessile mass near the isthmic portion was felt. This suggested a left hemiuterus.

*Course.* The pregnancy went to term and she delivered at the the maternity ward of the Aleman Hospital on September 28, 1936. A mechanical dystocia was caused by the septum of the vagina which did not allow the descent of the head of the fetus. A resection of the septum was performed. On hystero-graphy, the right uterine cavity did not visualize be-

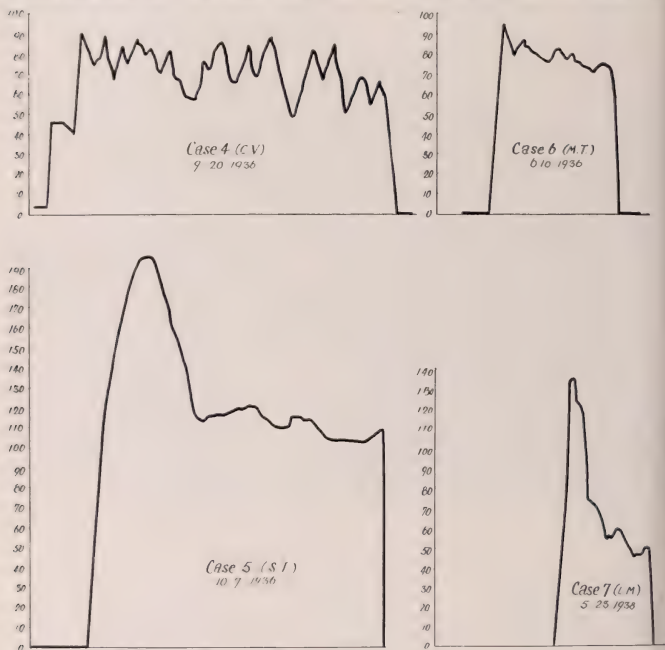


CHART II

cause of technical reasons. The clinical examination revealed at this time an uterus duplex unicollis with intrauterine septum which extended to the cervix. The exploration of the cavity with the hystrometer revealed both cavities divided by a septum. The hystero-salpingography (fig. 2D) visualized only the left hemiuterus. The tip of the catheter was not large enough to occlude the cervical canal because it was too broad. The catheter probably entered the left hemiuterus and obliterated the entrance of that hemiuterus. In fact, there was no reflux of Lipiodol, either to the other hemiuterus or to the vagina. The opaque substance outlined the tube of the left side. The insufflation (chart II) was positive at a pressure of 95 mm. Hg. The signs of permeability were positive.



*Case 7. History.* (Case of Dr. Derqui). L. M. complained of sterility.

*Examination.* There was a genital malformation with a vestibular anus. The insufflation was positive at a pressure of 130 mm. Hg. with a rapid fall of the pressure curve and revealed a continuous gas flow at a pressure of 60 mm. Hg. (chart II). Auscultation and classic shoulder pain established the uterotubal patency.

#### CONCLUSION

It is impossible to make definitive conclusions with such a small number of cases.

It is interesting to note that, except for case 3 which complained of sterility and which revealed partial occlusion, only in case 5 was a spasm of the tube overcome at a pressure of 210 mm. Hg., followed by an easy gas flow.

All other cases, and this is important to note, had absolutely normal graphs and were easily patent at very low pressures. They oscillated between 80 and 90 mm. Hg.

## DOES BACKWARD DISPLACEMENT OF THE UTERUS CAUSE STERILITY?

BETHEL SOLOMONS, M.D., F.R.C.P.I., F.R.C.O.G., F.A.C.S. (HON.)

*Gynaecologist, Dr. Steevens' Hospital,  
President, Royal College of Physicians of Ireland  
Late Master, Rotunda Hospital, Dublin  
(Dublin, Ireland)*

When I received the invitation to write for this commemoration volume in honor of Dr. Rubin, I was deeply gratified.

The discovery of tubal insufflation, as a method of diagnosis of patency, together with its value as a therapeutic agent in the cure of sterility, was a landmark in the history of gynaecology. It led to the discovery of the value of the Kymograph, and of salpingography. Rubin, the pioneer, is directly or indirectly responsible for all of these and has thus succeeded in bringing happiness to many homes.

I have been criticized for calling sterility a disease, but if the meaning of "disease" is ailment—sterility is a disease, and Hippocrates himself would have delighted in anyone who could aid in effecting a cure.

Memories now come back to me of our efforts to cure sterility when I was assistant to Tweedy at the Rotunda Hospital about 1909. At that time, we were performing salpingostomies, getting many bad results and a few good ones; and in cold blood—when we could discover nothing else, we opened the abdomen and blew up the tubes from the abdominal ostium with an ear syringe (fig. 1), and cures were obtained by this method.

When Rubin published his discovery, we wondered why we had not thought of it ourselves; but all great inventions, from wireless to insufflation, appear obvious after their discovery.

I found it difficult to decide in what way I could contribute to this volume. I had always been struck by the number of "doubting Thomases" who would not believe that backward displacement in itself was a very real cause of sterility; and a letter from a gynaecologist in England expressing his surprise that a patient who had come to Ireland and had had a subperitoneal Gilliam operation became pregnant soon afterwards, convinced me that there was a necessity for a short paper such as I present now. This patient had had every possible investigation made in regard to her sterility, and no success had been achieved. I am quite cognisant of the fact that a woman with backward displacement of the uterus can become pregnant, but I have definite knowledge that correction of backward displacement will cure sterility in many instances; and replacement should never be neglected. My delight is great when I find a fully retroflexed and retroverted uterus in a woman whose chief complaint is sterility, for it is well-known that the most difficult cases to cure are those where both the male and female are apparently normal in every way.

The question that must arise is—how does backward displacement cause

sterility? The spermatozoon has remarkable vitality but, in spite of this, it misses the way on many occasions if there are alterations in its usual route. If, therefore, the os uteri instead of pointing downwards and backwards, happens to point upwards and forwards the spermatozoon may take a wrong turning, and this is very definitely shown by the fact that a correction of retroflexion of the uterus so often results in the cure of sterility. Whether congestion of the uterus is a causal factor, I do not know: I doubt it strongly.

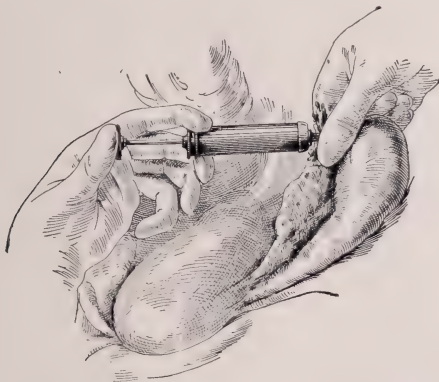


FIG. 1

In order to prove or disprove my belief I collected a small number of cases whose chief complaint was sterility and upon whom I had done the subperitoneal Gilliam operation for backward displacement of the uterus. The following questionnaire was sent out to them:

1. Have you become pregnant since your operation?
2. How many babies have you had?
3. Have you had any miscarriages?
4. Have you been well in every way?

Only the patients at Dr. Steevens' Hospital during the last ten years, as well as private patients over the same period, were considered. There were 207 in all: of these 28 did not reply, or the letters were returned because of change of address or some other reason. The average age was  $32\frac{1}{2}$ : the youngest was 22, and the oldest to become pregnant was 44. No patient was considered sterile unless she had been married at least  $1\frac{1}{2}$  years. The average number of years married was  $3\frac{1}{2}$ ; and in the successful cases the shortest period of marriage was  $1\frac{1}{2}$  years, and the longest 10 years. Nearly all these patients had been subjected to various types of hormonal treatment, and no effort had been made to correct the displacement. Needless to say, an investigation of the male was made in all possible cases.

## RESULTS

Among the 179 patients from whom answers were received 107 reported pregnancies, but 5 of these ended in abortion or miscarriage. It is difficult to say why the 72 others did not become pregnant: the obvious answer would be either that they required further investigation, or that the displacement was not the only cause of the sterility.

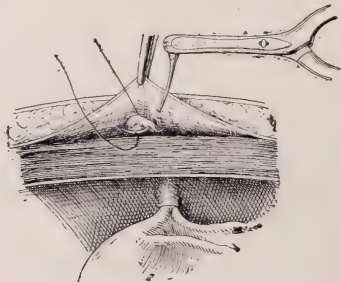


FIG. 2

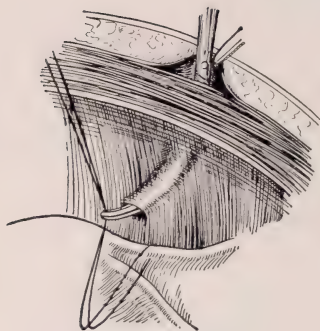


FIG. 3

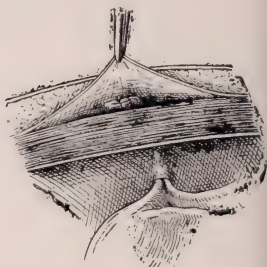


FIG. 4

The main and important factor is that 107 women became pregnant apparently as the result of the operation.

There was nothing special to report in regard to the other questions. The question, "Have you been well in every way?" brought a positive answer in 90 per cent of the cases.

In order to find out definitely whether backward displacement in itself caused sterility, a series of 50 cases with backward displacement was investigated.

These were all treated in various ways for sterility but nothing was done to cure the displacement; four of them became pregnant; the others are included in the series already described.

The operation which I have been doing for backward displacement is one which I myself devised many years ago. I have never seen it published except in my own *Handbook of Gynaecology*. It is absolutely safe from the pregnancy and labour point of view, and if properly done has no disadvantages. It is subperitoneal and, therefore, there is no possible chance of intestinal obstruction at any time. The technique is as follows:—

The abdomen is opened in the mesial line from the symphysis pubis upwards. Adnexal abnormalities are corrected. A stitch of No. 2 silk is placed about the round ligament on each side from 1 to 1½ inches (depending on the size of the uterus and the laxity of the ligament) from the uterine cornu; this stitch is not tied; silk *must* be used; if catgut is the material, a recurrence of the displacement will occur. A clip forceps is placed on the edge of the rectal aponeurosis on a level with the anterior superior spine of the ilium (fig. 2). A curved forceps is then passed under the aponeurosis between it and the muscle until it reaches the outside margin of the peritoneum. The forceps is passed outside and behind the peritoneum, and is then brought inwards until it reaches the stitch which has already been placed about the round ligament; it pulls this through. A Reverdin needle is then passed (fig. 3) through the under surface of the aponeurosis at the outer margin of the rectus muscle, through the thickness of the ligament, and is threaded with one end of the ligature, which is drawn through these structures; the same is done with the other end, and the stitch is tied. Figure 4 shows the operation completed on the right side. The same technique is carried out on the left side. The curved forceps may be passed through the internal abdominal ring, but there is no need to look specially for this point. The uterus is thus suspended in position by subperitoneal shortening of the round ligaments; therefore, there is no danger of intestinal obstruction. The silk is No. 2, and is sterilised as follows:

1. Wind loosely on glass reels.
2. Boil in water for ten minutes.
3. Store in 1 in 60 carbolic lotion.

The foregoing details are given because surgeons complain of trouble with silk. If care is taken in the sterilisation and there is no unnecessary handling, there should be no trouble.

It may be asked if treatment by replacement and insertion of pessary is ever carried out. The answer is in the affirmative but it has been observed on many occasions, that operation succeeded after pessary treatment had failed. It is difficult to know why this should occur; possibly the pessary acts in some way as a contraceptive.

#### CONCLUSIONS

- (1) Backward displacement of the uterus is a definite cause of sterility.
- (2) The result of a questionnaire is given.
- (3) The technique of a subperitoneal method of shortening the round ligaments is described.

I wish to thank Miss John at Dr. Steevens' Hospital for the trouble she took in sending out the questionnaire.

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## AN HISTORICAL REVIEW OF STERILITY

W. PELTON TEW, M.B., F.R.C.S. (Edin. & Can.), F.A.C.S. F.R.C.O.G.

(London, Canada)

### ANCIENT THOUGHTS ON STERILITY

Sterility has been regarded by most people for ages past as a very special misfortune and a curse. The Talmudists thought sterility and fertility depended upon the Will of God. In the Midrash Dēbārīm Rabbah, a dictum of the Rabbi Jonathan (1) is introduced which runs as follows "There are three keys in the hand of God, which none of his creatures can dispose of, neither an angel nor a seraph. These are the key of mortality, the key of the sterile, and the key of rain."

The Mohammedans, according to the will of Allah believed as follows, "God causes, according to his will, one woman to get girls, another boys, another children of both sexes, according to his will he also makes woman sterile" (1).

The customs of the Wachaga included the following rules in the case of a childless woman's death. "If a childless wife dies, she is thrown into the stream with all her things, her cooking pot, and her ladle. She is carried to the forest, or to some place that is never tilled. Also they do not take her corpse out by the door, but break a hole in the house wall on the opposite side, through which they carry her corpse and all her things. The bearers, her relations, receive three goats as a reward for all their labours. One of these is killed for her gratification." The corpse of the childless man also received similar treatment.

In some countries certain peoples believed that diet played an important role in sterility. The Fiji Island people believe that if a woman is sterile, she must have drunk the "water of sterility." In some parts of Japan they believed that women became sterile if they ate *akinasubi*. This is the late fruit of *Solanum* and contains little or no seed core. From this we might assume that the dearth of the seed core or germ element means there is a minimal content of Vitamin E which is found in the germ element.

The women in parts of equatorial Africa would not wash in the water of the White Nile, because they were afraid it would cause sterility. This belief is still common there today.

### ANCIENT BELIEFS IN THE PHYSICAL CAUSES OF STERILITY

Mohammed said "Choose a woman whose skin is brown for she is fertile in comparison with one who has a fair skin."

Hippocrates made the following comments on the causes of sterility: "1. Distortion and displacement of the uterus. 2. Too great smoothness of the uterine wall, so that the semen could not be retained. 3. Suppression of the menses, and obstruction of the upper part of the orifice of the uterus. 4. Overfilling of the uterus with blood and excessive secretion of menstrual blood which washes away the sperm. 5. Prolapse of the uterus in which its orifice

becomes hard and callous. 6. Unusually fat women do not conceive for the solid net of fat lying on the edge of the uterus presses it together, and so the uterus does not take up the semen."

In the Talmud we find physical signs being mentioned by which one can recognise a sterile woman, e.g. one may assume a woman to be sterile if she has reached the age of 20 and has no hair around the genitals, and has a male voice.

The ideas of Hippocrates have been preserved for a long time, even so late as the beginning of the 18th Century, and some traces are found today.

#### HOW DIFFERENT PEOPLES REGARD STERILITY

In Old German New Guinea a husband plays a wicked trick on his wife who scorns him by inflicting children upon her. In ancient Germany a husband could obtain a divorce if his wife bore him no children. There were no food or clothing problems in Germany in those days. However, even among the early Germans we find that many children could prove a burden, as we see such quotations as "A fertile woman will give you much care and much labour. A sterile wife is but one, but a fertile wife is a manifold burden of the house."

The ancient Hindus, because they had plenty of food, put a high value upon children. They had a law which said that if a woman produced no male children after 11 years of marriage she could be divorced. There are still similar customs among certain peoples.

In ancient Greece there was a law to provide for a substitute husband in any case where the male partner was at fault in childless marriages. This law was used mostly in cases where older husbands were married to much younger wives. The husband would choose the younger man whom he wished as his substitute. In most cases a blood relation of the husband was chosen in order to keep the family blood line intact.

The Oriental Jews made a childless marriage proper grounds for a divorce. The ancient Turks had a similar law. In southern India a childless wife brings her sister into her home to produce a family. If this is not possible the wife then returns to her family, or she agrees to marry an old man who does not want a family. The Chinese women are proud of large families. In Angola a childless wife is despised and she frequently commits suicide.

#### ANCIENT METHODS USED TO PREVENT STERILITY

A great variety of preventive measures have been resorted to throughout the past to prevent sterility. In many countries the first aim of the newly married couple was to produce a child. One can readily understand this after reading of some of the ridicule, or shame, or even worse punishment when a marriage proved sterile. Certain magic measures have been in use for years. Some of these magic measures are still in use today throughout the civilized and the uncivilized world on special occasions, such as the wedding day, the wedding night and the morning after the wedding.

In Aegina, immediately after the wedding, the marriage witnesses are accustomed to pelt the young bride with peas and pomegranate seeds, in order to

assure her fertility. Today we use rice and confetti. When the young wife entered her home for the first time, she must count the beams in the roof, and she would have as many children as there were roof beams.

The tent Gypsies in Transylvania, throw old boots and shoes at the newly married couple as they enter their tent, whereby the fertility of their marriage would be increased. We still see old boots and shoes suspended from the back of the automobile which is carrying the newly wedded couple away after the wedding ceremony is over.

The ancient Russians used only male animals for the meat to be eaten at the wedding. This was done in the belief that male meat would aid fertility.

#### ANCIENT MEDICINAL METHODS OF PROMOTING FERTILITY

Mandrakes (or love-apples) were used to promote conception in the early days, and we find mention of it in the Bible. (Genesis 30:14) "Rachel ate the mandrakes, but remained barren for years, whilst Leah became pregnant without the mandrakes." The tincture of the leaves of a perennial tree of the class Ternstroemiaceae has been used for years. In Algiers if a woman has one child and bears no more she must drink sheep's urine. In Western Australia the women eat a great deal of Kangaroo flesh to promote conception. In Bohemia the young wife drinks a tea made from Juniper berries.

The use of hot baths was advocated for years and is still used in many countries to promote conception. In Greece many springs and wells were used for this purpose. The Hindu Goddess Parvati became pregnant in a bath without having intercourse with a man. She gave birth to Ganesa. In Algeria famous hot baths are still used.

#### SUPERNATURAL HELP FOR STERILITY

This form of help has been in common use throughout the ages. In Ancient Rome sterile women directed their prayers to Juno Febralis (from februo, purify). In parts of China they worshipped Kwan-Yin, the goddess who brings forth children. Throughout various parts of the world we find many peoples seeking supernatural help for sterility problems.

In some countries supernatural human help is used to assist the sterile woman. There were and still are two temples of fertility in China. The priests in these temples are believed to be able to assist in a supernatural way.

#### LATER VIEWS ON STERILITY

In 1781 John Leake (2), M.D., physician to the Westminster Lying-in Hospital, wrote a book entitled "Chronic Diseases Peculiar to Women." In the chapter on abortion and barrenness he states "Women sometimes prove barren, or having conceived often miscarry. In proportion as they deviate from the simple law of nature in their manner of living, the vital powers of the body will be impaired. This more evidently appears by infirmities peculiar to women of superior rank, from which those of more humble stations are almost entirely free. The poor female cottager who uses exercise in the open air, who eats the

coarse but wholesome food and drinks from the cooling stream, is seldom troubled with those maladies which afflict the rich and indolent, undone by the abuse of plenty. Her body is not like that of the modern fine lady robbed of its native vigour by unseasonable indulgence or her mind tortured by imaginary wants; her nerves are not convulsed by insults of passion, or the excesses of midnight dissipation. So, far from being barren, she generally becomes the mother of numerous and healthy children, which like young oaks of the forest, planted by the hand of nature, without the imperfect artificial help of the nursery, by nature simply live and thrive."

In 1826 Dr. John MacKintosh (3) lecturing in Edinburgh, advocated the operation of dilating the cervical canal for cases of sterility. Since that time this operation has been used fairly extensively for cases of either primary or secondary sterility. I can personally recall a few cases that conceived after a dilatation.

Professor Pozzi (4) described an operation on the cervix called "Commissural Evidement" which consists of bilateral discission of the cervix in lengths of 2 to 3 cms., dilating the canal, and curetting. This is followed by stitching the mucosa of the cervical canal to the outer vaginal mucosa.

From those earlier days down to the present time we find womankind has ascribed her childless condition to a great variety of causes, and has used as great a variety of treatment. Today we believe we are approaching the subject more scientifically, and certainly we are. The results we are obtaining today are ample proof that much headway is being made. However, there still remains considerable to be done in this field. The influence of the endocrines on sterility and fertility is still in the realm of uncertainty, but in time this work will be covered and no doubt it will add still more to our present conception of the subject.

#### PRESENT DAY VIEWS

Numerous workers in the field of sterility and fertility have added considerably to our present day conception of these subjects. Among these workers we find that one man stands out eminently among the many others. That man is Dr. I. C. Rubin of New York City. On October 1, 1925, I. C. Rubin (5), M.D., F.A.C.S., delivered an address to the Section of Obstetrics and Gynaecology of the Royal Society of Medicine, London, England. His address was entitled "Diagnostic Value and Therapeutic Application of Peruterine Insufflation of the Fallopian Tubes in Cases of Sterility." In this address Dr. Rubin outlined the development of his momentous contributions on the subject of female sterility. He began his experimental investigation on animals in 1914. Collargol was injected via the uterus into the tubes and an x-ray picture was taken. He used Collargol, thorium, bromide and iodide solutions. He was, therefore, the first to use radiopaque substances for this purpose. These substances however at that time proved to be unsatisfactory because of the peritoneal irritations they caused. He therefore stopped the use of such substances and began to use gas or air for his injections.

The use of gas or air injections was started at the Mount Sinai Hospital,

New York in 1919. Oxygen was used on the first few patients. The gas was run in until the abdomen began to distend or the patient began to indicate considerable distress. An x-ray was taken and it disclosed a pneumoperitoneum. He used about 2 litres of oxygen for the first patient. From this first patient he learned the following lessons: (a) the amount of gas should be reduced; (b) a control was necessary; (c) a means of measuring the volume of gas to be used was necessary; (d) a smaller volume of gas could be used and demonstrated with the fluroscope.

Shortly after this Dr. Rubin substituted  $\text{CO}_2$  for oxygen.  $\text{CO}_2$  is more rapidly absorbed from the peritoneal cavity. He learned too that 150 cc. of gas or less did not cause any phrenic irritation or shoulder pain. Dr. Rubin now put all his experimental information together and designed his first complete apparatus for testing the patency of the Fallopian tubes. The apparatus could be used in the office. I personally purchased one of these early machines and used it for some few years. The details of the technique used for this type of insufflation may be readily obtained from a standard textbook or from one of Dr. Rubin's original articles.

Interpretation of the data obtained from the test is summarized as follows by Dr. Rubin.

1. Normal Tubes The mercury rises to 40, 60, or 80 or even 100 mm. and then drops 10 to 40 points, fluctuating several times until the cannula is withdrawn. Commonly the patient complains of slight pain referable to the uterus. The fluctuation in the pressure is said to be due to peristalsis.

2. Closed Tubes -If one tube is closed or stenosed, and the other normally open, the patient will complain of pain on the side of the tubal obstruction. If both tubes are stenosed or closed the pain is bilateral. This is due to distension of the tubes proximal to the point of obstruction, and is present whenever the latter is situated at any point beyond the isthmus. When the manometer rises to 200 mm. and uterine colic or midline pain referable to supra-pubic area is complained of, but no pain on either side, the closure is located at the intramural portion of the tubes, or near the isthmus on each side.

3. Spasm of the Tubes This is indicated when a fairly high pressure is reached, a drop is noted, indicating a small amount of gas has escaped through a minute opening. This behavior is interpreted as being due to tubal spasm.

#### THE CONTRAINDICATIONS AND DANGERS OF TUBAL INSUFFLATION

1. Evidence of pelvic or genital suppuration.
2. Pelvic tenderness.
3. Inflammatory masses.
4. Fever.
5. Uterine bleeding.
6. Serious form of cardiac, renal or pulmonary disease.

The danger of embolism can be easily dismissed providing the cases are properly selected and proper technique is carried out. Dr. Rubin has handed us some very noteworthy deductions from his experiences, regarding how to choose cases for the test and how to get good results.



- (a) Choose your cases carefully.
- (b) Use proper and meticulous technique.
- (c) The proper time to do the test is from 4 to 7 days after each period.
- (d) Repeat the test 3 or 4 times when necessary. The repeat tests may be done at monthly intervals or longer. When the tubes have been proven to be open, a repeat is not necessary.
- (e) The following menstrual period may come 2 or 3 days early.
- (f) The test may be used to check for patency after a tubal sterilization has been carried out.

Dr. Rubin (6) summarized much of his momentous work on this subject in a paper which appeared in the American Journal of Obstetrics and Gynecology in October, 1940. The title of this paper was "Utero-Tubal Insufflation as a Test for Tubal Patency, 1920-1940." In this article he gives the results of a questionnaire which involved 86,113 insufflation tests carried out in the United States and other countries. There was complete tubal obstruction in 30.88 per cent of cases and partial obstruction in 8.85 per cent. In Dr. Rubin's own series of 5,269 insufflations, there was complete obstruction in 32.4 per cent, and partial obstruction in 33.1 per cent.

A comparison of these two sets of figures is noteworthy. It shows a close accord in the percentage of total obstruction in the two groups but a wide difference in the partially obstructed cases. This difference is doubtless due to a variety of possibilities.

Other gratifying results of the Rubin Test are found in a paper by Rubin (7) in the American Journal of Obstetrics and Gynecology, December, 1945. In this article the author arrives at the following conclusions.

- (a) Among 2,014 patients in the primary sterility group, 358 or 17.8 per cent became pregnant following insufflation tests.
- (b) Among 1,186 patients in the secondary sterility group, 232 or 19.6 per cent conceived.
- (c) The therapeutic effect of the Rubin Test was proven definitely in 118 cases of tubal stricture, with pregnancy in 31 per cent as against 26 per cent of pregnancies in the cases of normal tubal patency.
- (d) 38.6 per cent of the patients became pregnant within two months after insufflation.

Testing for tubal patency is frequently done by injecting with a radiopaque substance. Several such substances have been used in recent years. As mentioned before, Dr. Rubin was one of the first to use such a substance but he discontinued its use because of the peritoneal irritation. At present Lipiodol is commonly used. Its chief disadvantage is that it remains for considerable time in the pelvis before disappearing. This however may be also an advantage, because it permits a picture to be taken several days or weeks after the injection whenever there is some doubt about the patency of the tubes at the time of the initial injection. Visco-Rayopake is a radiopaque contrast medium containing an organic iodine compound, and a polymeric form of polyvinyl alcohol. This substance seems harmless and it completely disappears within a few hours after the injection. Emboli may occur with Lipiodol injections, but they are seldom

fatal. An oil should never be used when there is any bleeding from the uterus, because of the danger of injecting some oil directly into one of the open sinuses or blood vessels.

There are still conflicting opinions whether the Rubin insufflation test or hysterosalpingography is the preferred method for testing tubal patency. The truth however seems to be that both tests must quite often be used on the same patient in order to arrive at the proper diagnosis. The following plan may be considered as the choice procedure for the average case to be tested. For the first test use a gas insufflation. If this is unsatisfactory try a second gas insufflation after giving the patient a sedative to relax any possible tubal spasm. If this second test fails or is unsatisfactory, then carry out a hysterosalpingography. Plastic tubal surgery should not be carried out without first resorting to hysterosalpingography.

After reviewing the history of the various studies on human sterility one readily concludes that Dr. I. C. Rubin's name stands today at the forefront of the many pioneer workers in this field. His conclusions have stood the test of time and remain sane and sound. He has guided us along the pathway with clarity and sound judgement. His contributions to his chosen work are indeed momentous and they reflect glory to himself and the profession in general. His articles are all clear, concise, and founded on fact. I admire all his writings for their conciseness and clearness. He did his work well and told us frankly how to do it and how to obtain good results. His name will be remembered for years to come for his wonderful contributions to gynecological achievements. Today there are thousands of happier parents in the world, and thousands of happy children as a result of Dr. Rubin's great work.

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# THE LIMITATIONS OF ENDOCRINE THERAPY IN MENSTRUAL DISORDERS

I. A. WIJSENBECK, M.D.

(Amsterdam, Netherlands)

*From the Department of Obstetrics and Gynecology, Endocrinological Clinic,  
University of Amsterdam*

Our recent knowledge of the physiology of menstruation has increased considerably. The same holds true, though to a lesser degree, of our knowledge of the abnormal menstrual process. As can be readily understood, many attempts have been made to influence the course of the abnormal menstrual cycle, founded on this better understanding, to which an extensive literature gives evidence. The literature devoted to the endocrine treatment of menstrual disorders has become so extensive that it can hardly be adequately surveyed. Moreover, it is so confused, that in setting out to form one's opinion from the literature, one is hampered by the many contradictory, critical and uncritical papers that have been written on the subject, so that it is difficult to separate the wheat from the chaff. The invitation to contribute to a volume in honor of Dr. I. C. Rubin, gives me a welcome opportunity to reflect on the course we have taken and to consider the results obtained.

Since we have a better understanding of the endocrine processes during the menstrual cycle—the production of the two gonadotropic hormones that are necessary for the elaboration by the ovaries of the estrogenic and corpus luteum hormones, with the resulting changes in the endometrium—our interest has been almost exclusively focused on the glandular changes in the endometrium. The rôle played by the other elements of the uterus, the blood vessels and the muscle fibers, in normal and abnormal bleeding, has remained in the background. Research in the last few years has thrown new light on these more or less neglected aspects.

From the investigations of Bartelmez in women (1933) and of Daron in anthropoids (1936) we know that the endometrium is supplied by two types of arteries. The larger arterioles between the muscle layer and the mucosa branch into two kinds of vessels: short ones that supply the basal layer of the endometrium and larger ones, the spiral arteries, that extend to just beneath the surface epithelium in the late secretory phase. The short arteries do not take part in the cyclic changes of the menstrual process; the spiral arteries however undergo typical changes during the menstrual cycle. These changes have especially become known by the experiments of Markee (1940), who transplanted bits of endometrium to the anterior chamber of the eye of monkeys. The changes in the bloodstream of the arterioles and the constriction of these vessels are influenced by the activity of the uterine musculature. Older investigators (Keiffer, Bucura, Joachimowitz) knew the importance of the muscle fibers that surround the arteries on their way through the uterine muscle to the endometrium and their influence on the amount of blood lost during menstruation. Westmann cor-

rectly stresses the influence of the changes in uterine contractility on the flow, as a factor in the mechanism of menstruation that is all too often forgotten. In the pre-hormonal era gynecologists, in the treatment of abnormal uterine bleeding, almost exclusively used drugs that promoted the contractions of the uterine musculature. In the current hormonal era these drugs have become almost obsolete. In view of the newer understanding of the rôle of uterine musculature in the regulation of the menstrual flow it is well to be careful not to throw the handle after the hatchet.

Another important factor in the regulation of normal and abnormal menstrual bleeding, although generally known and recognized, has had little attention in the treatment of menstrual disorders, i.e. the great influence of mental stimuli. It is highly interesting that this fact, which has been recognized for centuries and is theoretically accepted by everyone, in practice seems to escape attention at a time when psychosomatic medicine is the focus of medical interest. Every gynecologist acknowledges that emotional disturbances often find their expression in the sexual sphere and yet, this connection between psyche and soma is almost completely neglected when these same clinicians publish papers on the treatment of functional uterine bleeding. Every clinician knows that young girls, merely from fear of being pregnant, cease to menstruate; that women who ardently desire pregnancy, may demonstrate the phenomenon of "false pregnancy," consisting of amenorrhea, distension of the abdomen and pigmentation of the nipples, phenomena that can only be brought about by endocrine changes, but which are induced by psychogenic stimuli. Recent publications on war amenorrhea in prisoner camps all agree that in these instances amenorrhea occurred so promptly, that not dietary but only mental influences can explain it. Even a normal flow in a woman with usually normal menstruation may suddenly be interrupted by temporary emotional disturbance and a premature onset of menstruation is known to occur in women who have an unconscious aversion to intercourse and who use this method to avoid it. Long articles have been written on dysmenorrhea occurring in young girls who were mentally unprepared for the approaching event or in girls after difficulties in school or in love affairs. Nevertheless one would search in vain for the evaluation of these psychic factors in practically all clinical papers dealing with the treatment of all types of menstrual disorders by all kinds of hormones now at our disposal. It seems to me that a good many of the reported successes, which we are unable to explain with our theoretical knowledge of the function of these hormones, must be ascribed to psychic influences. On the other hand, many a result which could reasonably be expected, is not obtained owing to the neglect of such psychic factors.

There is still another difficulty by which we are hampered in our treatment of menstrual disorders, especially in the ambulatory patient. For the therapy of menstrual disorders it is just as indispensable as in the treatment of any pathologic condition, to have the diagnosis established before starting treatment. However, it is still very difficult to diagnose correctly the underlying endocrine disturbance. Much would have been accomplished were we able to get an insight in the endocrine functions of the ovaries and the anterior pituitary by determining the hormonal concentration in the blood and their output in the

urine. But here we are faced by great practical difficulties. Such an assay in the laboratory is not only far from being a simple matter, but each particular case requires a whole series of such determinations, so that in practice endocrine treatment is usually begun without even trying to secure these data. Two other methods by which we may indirectly gather some knowledge of the functional state of the ovaries—endometrial biopsy and the vaginal smear—are not so reliable that they can fully replace hormonal assay.

Being fully aware of and accepting these existing limitations, what can we now achieve with endocrine treatment in the various menstrual disorders?

#### AMENORRHEA

Let us assume that a careful investigation has demonstrated that amenorrhea—which is after all a symptom and not a disease—is not caused by exhaustion, anemia or hypothyroidism; that no nutritional disturbances which comprise cases of over-eating as well as of under-nourishment are evident; that no ovarian tumors with endocrine function, no symptoms of the syndrome of Cushing, Froehlich or Simmonds or of the genito-adrenal syndrome are present; that no pathologic condition of the uterus is responsible, in short that no demonstrable organic cause exists. What then can we obtain with endocrine therapy? Having excluded the above mentioned factors we shall have to assume that either the gonadotropic hormones are absent or inadequately produced by the pituitary, or that the ovaries are, primarily or secondarily, refractory to the gonadotropins. I know of no hormone capable of stimulating the gonadotropic activity of the pituitary, nor of any such substance capable of bringing the ovaries out of their state of refractoriness. The only thing we can do where the endogenous gonadotropins are lacking, is to try and replace them by injecting one of the commercial products. Are these gonadotropic hormones capable of stimulating the resting endocrine activity of the ovaries? There are three commercial products at our disposal: FSH the follicle stimulating hormone prepared from the anterior lobe of the hypophysis, APL the anterior pituitary-like hormone formed by the chorion and prepared from the urine of pregnant women and a gonadotropin which is extracted from the serum of pregnant mares. The first hormone of which theoretically we could have the greatest expectation, is not yet available in sufficient amounts and concentrations to be of practical value. It is generally accepted that chorionic gonadotropin, which aroused such great hope after Zondek's publications on prolan, is not able to bring follicles to maturity in women. According to Geist it even produces an arrest of follicular development. The expected results were similarly not obtained by a combination of chorionic gonadotropin with a synergist from the hypophysis itself, which has been recommended by some clinicians. The serum gonadotropin in its action lies midway between the two other hormones, but its application also proved disappointing, after it had been enthusiastically received, following the positive evaluation of Davis and Koff. It is only able to produce ovulation in ovaries that are capable of spontaneous ovulation; in cases of amenorrhea it proved incapable of activating the resting follicles.

What can be expected from the treatment of amenorrhea with estrogens?



Their action on the hypophysis is an inhibitory one and we gratefully avail ourselves of this influence in the suppression of lactation and in the treatment of the menopausal syndrome. Moreover, it is certain that estrogens do not stimulate the hypophysis, not even in the small quantities that have been advocated. And as far as an eventual action on the ovaries is concerned, estrogens like other hormones fail to stimulate the organ that produces them: insulin does not act on the pancreas, thyroxin is inactive with the thyroid and adrenalin does not effect the adrenals. The only influence of estrogens on the ovaries is an inhibitory one, via the suppression of the gonadotropic activity of the anterior pituitary. A treatment of amenorrhea with gonadotropic hormone, although physiologically justified, is not yet possible because we do not dispose of an active gonadotropin; treatment with estrogens however is, according to our belief, irrational.

The only value of estrogens in the treatment of amenorrhea is their capacity of developing the resting endometrium, not via hypophysis or ovaries, but through direct action on the uterus. If the administration of estrogens is stopped, the proliferated endometrium is cast off, accompanied by bleeding; a so-called withdrawal bleeding occurs. Thereafter, however, the amenorrhea persists unchanged. Such withdrawal bleeding can be of great psychic significance for girls or women who suffer from a sense of inferiority due to their amenorrhea. After such bleeding, which is an anovulatory menstruation and cannot be distinguished by the patient from normal cyclic bleeding, they again feel like normally functioning women. There is no question of a cure; it is no more than a temporary substitution therapy.

I know that notwithstanding the fact that we cannot expect any success from treatment with estrogens, we repeatedly hear claims of permanent results from such substitution therapy, results continuing after the cessation of treatment, especially in those cases where simultaneously progesterone was given and the cyclic administration had imitated the normal menstrual cycle. But we have to remember that these same favorable results were reported at a time when the available concentration of estrogens and the injected quantities were so ridiculously small—at best 10–20 international units—that any other than a mental effect could not reasonably be accepted; or when aqueous ovarian extracts like agomensine were given, which did not contain any hormonal substance. Naturally no one can deny the reported results but it would still have to be proved that they were due to the specific effect of the substances administered.

#### FUNCTIONAL UTERINE BLEEDING

The outlook in the treatment with endocrine substances in functional bleeding is more promising. Here we are less hampered by diagnostic difficulties, for in many cases endometrial biopsy shows hyperestrinism to be present and of causal importance. Usually we distinguish between menorrhagia or hypermenorrhea, in which the cycle remains undisturbed and only the quantity of blood or the duration of the bleeding or both have increased; and metrorrhagia or polymenorrhea where the regular cycle no longer exists, but irregular bleedings

occur, in which the amount of blood and the duration of every bleeding can or cannot be increased. Of late there is a tendency to change this classification into one where the different types of bleeding are distinguished into the ovulatory and anovulatory.

It is generally accepted that functional menorrhagia is caused by an imbalance between estrogen and progesterone, with estrogen formed in too great or progesterone in too small a quantity. When there is reason to assume a deficiency of progesterone, the logical procedure is the administration of progesterone, either by injection or orally in the form of pregnenolone, with which treatment good results have been obtained. If an excess of estrogen exists, the male hormone testosterone, has come to be accepted of late as a means to check the bleeding. The mode of action of the male hormone in these cases is not yet clear: it may act through inhibition of the anterior pituitary with the resulting suppression of estrogen formation, or it may, like progesterone, neutralize the influence of estrogen on the endometrium, or be converted into progesterone with which it is chemically closely related. We are now able to cure with either of these two hormones most cases of functional menorrhagia which were formerly such a problem for the gynecologist.

The bleeding in functional metrorrhagia, which usually is of the anovulatory type, can occur from an atrophic, proliferative, or hyperplastic endometrium. This would indicate that in this type of bleeding there may be question of a shortage or excess of estrogen and a lack of progesterone. Good results have been reported with progesterone therapy that compensates for the existing deficiency, or with the administration of chorionic gonadotropin, that may not have a follicle stimulating effect on the ovaries, so that it cannot be used in the treatment of amenorrhea, but that in large doses seems to have a certain luteinizing effect and thus stimulates the ovaries to produce their own progesterone.

Illogical though it seems, there is an increasing tendency to treat functional metrorrhagia with estrogens (Hamblen). Its effect is explained in this way: the endometrial hyperplasia is brought about by estrogens that are continuously formed, but in small amounts, by the cystic follicles. This uninterrupted action of estrogen is inadequate for a healthy growth of the mucosa. The amount of estrogen necessary for an adequate growth stimulus can be furnished by injection. When these injections are stopped the sudden lowering of the level of estrogen in the blood causes a breakdown of the endometrium which is cast off and the bleeding ceases. Moreover, through the inhibitory effect on the hypophysis a period of rest for the ovaries can be induced. Androgens are similarly used in the treatment of metrorrhagia with equally good results as in the treatment of menorrhagia.

#### DYSMENORRHEA

Of all menstrual disturbances dysmenorrhea is the most eloquent example of the great influence which mental factors have on the pain as well as on the eventual success of therapeutic measures. Various theories concerning the cause of dysmenorrhea have been accepted in turn and good results have been

obtained through methods of treatment based on a variety of theories. This should not surprise us, for "the sequence of contradictory theories, therapeutic success by opposing technique and subsequent recurrence is one, which we are beginning to recognize, bespeaks the psychosomatic disease or at least the disease in which psychological factors play an outstanding role" (Gill). At present, in the era of endocrine etiology of dysmenorrhea, hormonal treatment is exalted. The choice of the various hormones depends on the question as to which hormonal factor is held responsible for the initiation of the painful uterine contraction, for opinions agree that the cause of primary dysmenorrhea is hypercontractility of the uterine musculature. Many years ago Knaus pointed out that the corpus luteum hormone has an inhibitory effect on uterine contractility; this hormone has been used by many clinicians to reduce the excessive contractions in cases of dysmenorrhea and there are many favorable and even enthusiastic reports about this method of treatment.

Those who stress not so much the lack of progesterone, but emphasize the preponderance of estrogen—estrogen being the hormone that is responsible for the normal uterine contractility—are equally pleased with the use of testosterone as a means of suppressing the influence of the estrogens.

There is, however, another group of clinicians who reason quite differently. According to them there is not only no lack of progesterone, but their experiments indicate that dysmenorrhea only occurs in cycles where a corpus luteum has been formed. In anovulatory cycles they never found menstruation to be painful. So instead of being considered as a beneficent agent to regulate excessive contractions, progesterone is held responsible for just this hypercontractility. The adherents of this theory support it, by recalling the old observation that young girls, shortly after the menarche, when the cycles are still anovulatory, usually menstruate without pain and that only after some time, when the anovulatory cycles have been replaced by those in which a corpus luteum is formed, dysmenorrhea becomes distressing. Moreover, juvenile or premenopausal metrorrhagia, conditions admittedly characterized by the absence of corpus luteum formation, are always painless. Consequently they treat dysmenorrhea with estrogens, which, when given at the appropriate time, i.e. in the first half of the menstrual cycle, and in sufficient quantity, will prevent the next ovulation and so prevent the formation of a corpus luteum. They claim that the following menstruation invariably is free from pain. Another explanation of the beneficial action of estrogen has been offered by the physiologist Reynolds. It is a well known fact that dysmenorrheal pain is of the sympathetic type. Estrogens however have a parasympatheticomimetic action. A deficiency of estrogens will inhibit the parasympathetic system, and diminish the production of acetylcholine. In consequence there is overactivity of the sympathetic nervous system, with the production of vasoconstrictor substances and the occurrence of pain.

I have mentioned three theories, all of which explain dysmenorrhea on an endocrine basis. Three hormones have been recommended with equal enthusiasm for the relief of dysmenorrheal pain. I think we are justified in stating that

it is reasonable to assume that it is not the administered substances that are all important, but that the psychic make-up of the patient and the influence emanating from the doctor are two factors which at least are equally responsible for the success obtained.

The science of endocrinology and the possibility of its practical application in menstrual disorders are relatively recent. As this discussion shows much has still to be learned and perhaps new paths may be found. In the near future improvement of diagnostic possibilities perhaps by simplification of the methods of assay, more consideration of psychosomatic aspects in the etiology of menstrual disturbances, and more research on the role of the blood vessels and of the musculature of the uterus in connection with the abnormal flow may considerably change our present therapeutic approach.

## INFECTIOUS HEPATITIS IN PREGNANCY

BERNHARD ZONDEK, M.D. AND Y. M. BROMBERG, M.D.  
(Jerusalem, Palestine)

*From the Obstetric and Gynecological Departments of the Rothschild-Hadassah  
University Hospital*

Infectious hepatitis is generally considered a benign disease occurring in sporadic or epidemic form. Until the last war its sporadic form was known under the name of catarrhal jaundice, and its etiology by contamination with a specific infectious agent has not been admitted. During World War II the disease spread in epidemics throughout many countries and assumed proportions hitherto not experienced (1). This widespread wave of jaundice gave numerous workers excellent opportunity to study the epidemiological and clinical aspects of the disease. It has been shown, as a result of these extensive investigations, that the icterogenic specific agent of infectious hepatitis is a filtrable and heat-stable virus (2) and that transmission from man to man generally takes place through direct or indirect contamination with feces of persons suffering from the disease (2, 3 and 4). Furthermore, the incubation period was estimated to last from 8 to 42 days, although in the majority of cases the disease appears in about 30 days after contact with contaminated material (2, 3 and 5). The clinical features and course of infectious hepatitis have been divided into three stages: preicteric, icteric and convalescent (6, 7 and 8). The liver function tests were thoroughly investigated during all phases of the disease and although the maximum deviations from normal were present during the icteric stage (9), functional liver impairment has been found to persist several weeks after clinical recovery (8 and 10). It has also been stressed that the disease, although benign, may exceptionally be rapidly fatal. In fact one death from acute liver necrosis occurred in a series of 300 cases of infectious hepatitis (5), while three others have been observed in a series of 1062 cases (11). Chronic hepatitis resulting from residual damage to the liver after acute infectious jaundice, has also been described (12). The outbreak of infectious hepatitis in different theaters of war was also accompanied by widespread epidemics among civilian communities (1, 3 and 5). (As an example, the incidence in Norway among civilians was 1-4 per cent during the 1943 epidemic.)

Surprisingly few data (13 and 14) have been reported during recent years when this disease complicates pregnancy. This may be due to the relatively rare occurrence of infectious hepatitis in pregnant women, both in its sporadic form [10 cases of jaundice in 72,000 pregnant women were observed in the Chicago Lying-in Hospital (15)] as well as in its epidemic form [during the Swedish epidemic of jaundice in 1927 with high incidence of acute hepatic atrophy, no case of the disease was noted in pregnant women (16)]. However, the disease is known to be particularly dangerous when occurring in pregnant women in its epidemic form, frequently leading to death from acute liver necrosis generally preceded by abortion or premature delivery (13).



In Palestine a particularly widespread outbreak of infectious hepatitis among civilians began toward the end of 1941. The incidence of disease was estimated to be 3-4 per cent of the Jewish population (17). The course of the disease was generally benign; however, cases with fatal outcome have been observed almost exclusively in pregnant women (18).

It should be emphasized that there is a tendency among obstetricians to consider infectious hepatitis in its sporadic form (hitherto known as catarrhal jaundice) as an essentially benign disease never leading to serious complications. In those cases, which are rapidly complicated by acute necrosis of the liver, the infectious etiology seems to be often overlooked. Such cases are generally classified as a form of toxemia of pregnancy. This frequently led to misinterpretations in the diagnosis and prognosis.

Our interest in the study of infectious hepatitis in pregnancy began in October 1943, when a seven months' pregnant icteric patient in a comatose condition due to acute atrophy of the liver was admitted to this hospital. The question arose as to whether the patient suffered from a special form of toxemia pregnancy or from infectious hepatitis complicated by acute atrophy of the liver. We could solve this question in favor of the latter possibility, since evidence of prolonged contact between the patient and some members of her family suffering from jaundice had been established. When during successive weeks new cases of jaundice in pregnancy were admitted, it became clear that we were dealing with an outbreak of infectious hepatitis.

It is our desire in this paper to describe the clinical picture of infectious hepatitis in pregnancy and to correlate its symptoms with the laboratory data of liver function<sup>1</sup>; to study the influence of infectious hepatitis on pregnancy, labor and the puerperium, and on the state of the new-born; to consider the factors contributing to the particularly severe course of infectious hepatitis during pregnancy; and to report upon therapy, with special reference to obstetrical treatment.

#### MATERIAL

This study comprises a series of 29 unselected women, who developed infectious hepatitis during the course of pregnancy. These women were observed during the period of 32 months, from October 1943 to July 1946. It is noteworthy that during the preceding 9 years (1934-1943) only two cases of infectious jaundice (then termed "icterus catarrhalis") and one case of acute liver atrophy have been observed in 12,360 pregnant women delivered in the obstetrical department of the Hadassah University Hospital (an incidence of 0.016 per cent and 0.008 per cent respectively). The present series of 29 cases of infective hepatitis were observed in 3,382 pregnant women, an incidence of 0.85 per cent, which is fifty times greater than that of the preceding series. The patients described in this paper belong to different social and economic groups; however the majority (18) were definitely undernourished, their food intake being particularly low in proteins. Twelve of the patients came from the same district of Jerusalem, where hygienic facilities are particularly poor. Seventeen cases (5 per cent) occurred in the last three months of every year (October, November, December), when the incidence of the disease among the general population was also high. The course of the disease during this season of the year was particularly severe. There

<sup>1</sup> Laboratory findings in infectious hepatitis in pregnancy will be published in detail separately.

were 8 primiparas and 21 multiparas of various ages ranging between 18 and 40 years. In 6 women the disease occurred during the first half of pregnancy, in 19 during the second half, and in 4 during the puerperium. The patients were admitted to the hospital in different phases of the disease; 6 during the preicteric stage and 23 during the acute icteric stage.

The laboratory tests<sup>2</sup> used in this work were principally concerned with the excretory and secretory functions of the liver in relation to its endogenous physiological products, since liver tests based on the excretion of foreign, exogenous substances (e.g. hippuric acid test (19), bromsulfalein test (20), etc.) frequently give inconsistent results in pregnancy. (The hippuric acid test was used in this study in patients recovered from infectious hepatitis in order to detect residual liver damage; it was performed 2 or 3 months following delivery or abortion.)

The following laboratory tests were found to be of particular value in this study. 1. Determination of the ability of the liver to deaminate amino-acids by analyses of a) urea, b) amino-acids and non-protein nitrogen in the blood. 2. Determination of disturbances in plasma protein formation by analyses of a) albumin and globulin fractions, b) cephalin-cholesterol flocculation tests and c) the Takata-Ara reaction. 3. Determination of disturbances in blood cholesterol formation and esterification by total cholesterol and cholesterol-ester blood values<sup>3</sup>. 4. Determination of disturbances in carbohydrate metabolism by analysis of fasting blood sugar.

*Clinical aspects of infectious hepatitis in pregnancy etiology.* The outbreak of infectious hepatitis in the present series was strictly related to the widespread occurrence of the disease in the population as a whole. Contamination by contact with non-pregnant icteric individuals was ascertained in 12 cases. No exact data, however, as to the duration of the incubation period could be obtained, because of the multiple contacts between the patients and their relatives suffering from jaundice. Of particular interest is the fact that non-pregnant individuals affected by hepatitis, and considered as the source of contamination in many of our cases had a mild form of jaundice. On the other hand, some pregnant women, who contracted the disease from them, died of acute necrosis of the liver following a particularly severe clinical course.

The above observations lead to the assumption that in infectious hepatitis occurring in pregnancy, certain aggravating factors affect the clinical course of the disease. These latter will be discussed below.

*Clinical manifestations of infectious hepatitis in pregnancy.* Since the outstanding feature in our cases of infectious hepatitis in pregnancy was the extreme variation in the severity of the clinical course and laboratory findings, the cases will be described in three different groups (A, B and C). In this description special attention will be given to the severe cases (group C), which frequently exhibited a tendency to the development of acute liver atrophy. The reader interested in the frequency of the various manifestations of the prodromal and acute stages of the disease, in all three groups is referred to Tables I and II.

*Group A: Hepatitis without jaundice.* This group comprises two cases (7 per

<sup>2</sup> We are deeply indebted to Prof. E. Wertheimer, Head of the Chemical Laboratory of Hadassah University Hospital, for his personal interest, kind advice and assistance in this investigation and to Mrs. J. Bendersky, M.Sc., assistant in this laboratory.

<sup>3</sup> The average normal values for plasma cholesterol in pregnant women are as follows: Cholesterol total 205 mg. per cent, free cholesterol 63 mg. per cent, cholest. ester 140 mg. per cent, free/ester ratio 0.45.

cent) of particularly mild infectious hepatitis in pregnancy in which there was no clinically manifest jaundice, but transitory bilirubinuria was demonstrated. The clinical symptoms were particularly mild and laboratory tests showed only slight impairment of the liver. In both these pregnant women the symptoms were limited to anorexia, nausea, constipation and slight pains in the hepatic area, accentuated by percussion over the liver. The liver was slightly enlarged, but the spleen was not felt below the costal margin; the sclerae were slightly subicteric in both patients but no manifest jaundice appeared during the course of the disease which lasted respectively 8 and 10 days. The icterus index at its peak values was respectively 15 and 20, and slight positive direct van den Bergh reaction was present in both cases. All tests of liver function mentioned above gave normal results, except for the cephalin-cholesterol flocculation test which was positive in both patients.

Although only 2 cases of infectious hepatitis without jaundice have been observed in our series, we feel that similar cases may occur much more often. Their detection depends largely on proper examination of pregnant women during epidemics. In fact, the frequent occurrence of this form of hepatitis, unrelated to pregnancy, has been emphasized by other authors (8 and 12).

*Group B: Infectious hepatitis in pregnancy with a moderately severe clinical course.* This group comprises the majority of our patients (18 cases—62 per cent). These patients exhibited symptoms similar to those usually observed in infectious hepatitis when not in pregnancy, but laboratory evidences of serious liver damage were more frequent. However, certain manifestations characteristic of infectious hepatitis occurring in pregnancy should be stressed.

The onset of the disease was insidious, the early manifestations of asthenia, anorexia and nausea were generally interpreted by the patients as disagreeable but common phenomena of pregnancy. Vomiting was a frequently observed symptom (table 1), but in the majority of our cases was not recognized as a precursor of infectious jaundice, owing to its frequent occurrence in normal pregnancy. In one of our cases in the third month of pregnancy, the vomiting of the preicteric stage followed hyperemesis of pregnancy. Jaundice, which subsequently developed, could be considered as a complication of pernicious vomiting of pregnancy, but definite evidence of contamination by contact with other icteric individuals was found.

The outstanding symptoms during the icteric stage were liver tenderness and liver enlargement. Itching and bradycardia was surprisingly rare and observed in two patients and only for short periods. Signs of vitamin B deficiency, such as glossitis and angular stomatitis, were frequently observed (table 2).

The liver function tests performed in these patients indicated serious liver functional impairment: hypoproteinemia with particularly pronounced decrease of the serum-albumin fraction was observed in 9 of 18 cases of this series. A strongly positive cephalin flocculation was found in 12 cases and a positive Takata-Ara reaction in 12 cases. The decrease in the amount of total blood cholesterol with an especially pronounced depression of the ester-fraction was found in 13 of the 18 cases of this group. Low fasting blood sugar levels were

TABLE 1

*The frequency of symptoms during the preicteric or prodromic stage  
(29 cases)*

SYMPTOMS	NUMBER OF CASES	PERCENTAGES
Anorexia .....	29	100
Nausea .....	29	100
Asthenia .....	29	100
Vomiting .....	19	65
Pains in hepatic area .....	18	62
Constipation .....	17	58
Heartburn .....	16	55
Headache .....	12	41
Fever .....	9	31
Arthralgia and myalgia .....	8	28
Diarrhea .....	1	3

TABLE 2

*The frequency of symptoms in the whole series and their distribution in the 3 clinical groups  
during the icteric or acute stage  
(29 cases)*

MANIFESTATIONS	NUMBER OF CASES	PER CENT OF CASES	GROUP A*	GROUP B†	GROUP C‡
Anorexia .....	29	100	2	18	9
Nausea .....	29	100	2	18	9
Vomiting .....	29	100	2	18	9
Asthenia .....	27	93		18	9
Evident jaundice .....	27	93		18	9
Glossitis .....	21	72		12	9
Tenderness of liver .....	20	69	2	18	
Constipation .....	19	65		12	7
Edema of legs .....	17	58		8	9
Enlargement of liver .....	16	55	2	14	
Fetor hepaticus .....	9	31			9
Psychic disturbances .....	9	31			9
Reduction of liver size .....	9	31			9
Enlargement of spleen .....	8	28		6	2
Hepatic coma .....	5	17			5
Herpes labialis .....	4	13		1	3
Fever .....	3	10			3
Epistaxis .....	3	10		1	2
Itching .....	2	7		2	
Bradycardia .....	2	7		2	
Bronchitis .....	2	7			2
Uterine hemorrhage .....	2	7			2
Convulsions .....	2	7			2

\* Group A: Hepatitis without jaundice (2 cases)

† Group B: Moderately severe cases (18)

‡ Group C: Severe cases (9)

found in 12 patients, while definite hyperglycemia was present in one case. No abnormalities, however, in the urea and amino-acids blood concentration could be found in the moderately severe cases.

Sixteen patients of this group (88 per cent) recovered completely when examined 6 months after their discharge. One patient died from a fulminant intraperitoneal hemorrhage following uterine rupture during delivery. This death was directly related to an obstetrical complication and cannot be taken in consideration in the mortality rate of infectious hepatitis in pregnancy. In another woman of this group residual liver damage manifested by signs of chronic hepatitis was found 18 months after recovery from the acute stage of jaundice.

In summarizing it may be said that infectious hepatitis in pregnancy in its moderately severe form, differs from the usual form of the disease by: 1) the high incidence of vomiting and manifestations of vitamin B deficiency, 2) the rare occurrence of itching and bradycardia and 3) the frequent occurrence of hypoproteinemia, positive cephalin and Takata-Ara reactions, depression of the cholesterol-ester formation and low sugar blood levels.

*Group C: Infectious hepatitis with a severe clinical course and a tendency to acute atrophy of the liver.* Nine patients of this series (31 per cent) had a particularly severe clinical course, which in 5 led to death from acute atrophy of the liver. Laboratory studies in all these patients showed grave impairment of hepatic function and advanced damage of the liver.

The following general symptoms, physical and laboratory findings, present in all cases, pointed to the severity of the disease:

a) *General symptoms.* Pronounced psychic instability was observed in all patients of this group. Although apathy and lack of interest in their surroundings prevailed, there were sometimes periods of irritability and increased nervous tension due to anxiety.

Subsidence of the pains in the liver area. Pain in the hepatic area, spontaneous or evoked by liver percussion subsided rapidly after the appearance of jaundice in all severe cases. This may be due to the atrophy of the liver, since these pains have been attributed to the distension of the liver capsule by an enlarged liver during the first phase of hepatitis (22).

"Fetor hepaticus," the specific breath of patients with acute liver necrosis, was observed in all nine women of this group. In the 5 women who died the hepatic fetor persisted until death, while in 4 patients who recovered this sign was observed during a short critical period of the disease.

b) *Physical findings.* Tachycardia. Although bradycardia is a generally accepted sign of jaundice, these nine severely ill women exhibited definite tachycardia. Tachycardia was particularly pronounced in the five cases with fatal outcome. It appears that the finding of a constantly rapid pulse rate in infectious hepatitis in pregnancy should be considered as an unfavorable prognostic sign.

Progressive reduction of the size of the liver. This was established by frequently repeated percussion and was considered as the most important diagnostic and prognostic sign in this group. It should be emphasized that this examina-



tion is greatly hindered by the pregnant uterus in cases of advanced pregnancy and experience is required to determine the liver borders. In all cases the extent of hepatic dulness was determined at the first examination, and in the course of the disease changes in the size of the liver were followed by repeated percussion. In those five pregnant women in whom the disease had a fatal outcome the area of hepatic dulness rapidly decreased and disappeared entirely during hepatic coma. In the women who recovered, hepatic dulness returned to normal with surprising rapidity.

In one case, observed from the beginning of the disease, an enlarged and tender liver had been found at the onset of jaundice. During the acute stage, rapid reduction size of the liver was observed; simultaneously tenderness of the liver vanished and hepatic fetor was noticed; during the subsequent two days, hepatic dulness was completely absent, the patient being in a subcomatous condition. On the third day the general condition improved, the area of hepatic dulness reappeared and seven days later the liver edge was distinctly felt under the right costal margin. In this case it was possible to determine, not only the rapid shrinking of the liver during the acute stage, but also its amazing power of regeneration during recovery.

c) *Laboratory findings.* In all these women there was extensive hepatic damage, the liver being frequently unable to perform its most important functions.

α *Progressive decrease of urea blood level.* We observed in 8 of these 9 patients a sudden drop in blood urea level simultaneously or even preceding the aggravation of the clinical symptoms. In five cases, with fatal outcome from acute atrophy of the liver, the drop in the urea blood values was observed a few days before the onset of hepatic coma and only "traces" of urea could be found in the blood shortly before death (table 3, case IX). In three other cases of this group the blood urea concentration dropped to 4.8 mg. per cent (table 3, case XVII), 7 mg. per cent and 10 mg. per cent; these women recovered despite the additional unfavorable prognostic signs of *fetor hepaticus*, tachycardia, and reduction of liver size. The finding of a low blood urea level in serial examinations in an icteric pregnant woman should be considered as a sign of widespread hepatic damage and arouse the suspicion of acute liver necrosis.

In two women who died from acute liver atrophy the progressive decrease in urea blood level was associated with a rise of amino-acids (10-11 mg. per cent) and with slightly elevated values of non protein nitrogen (38-40 mg. per cent).

β *Hypoproteinemia.* Low protein blood values with especially depressed levels of the albumin fraction were found in 8 cases. Such findings point to the severity of the disease only when associated with other symptoms, since equally pronounced hypoproteinemia was also found in 9 milder cases of infectious hepatitis in pregnancy (group B).

γ *Cephalin test.* The cephalin test was positive in all severe cases and became gradually stronger when the clinical condition deteriorated; on the other hand, the reaction became rapidly negative during the recovery stage. Since strongly positive cephalin test was also observed in patients with milder forms of hepatitis (group B), it cannot be considered of great prognostic value.

δ *Blood cholesterol.* The decrease in the amount of total cholesterol with definite depression of the ester fraction was found in five cases. In three of five women who died from acute liver atrophy, rapidly decreasing total cholesterol and cholesterol ester values, and even absence of blood cholesterol ester, were found 1 or 2 days before death. In two other women, however, who died from acute liver atrophy, there was no depression of cholesterol blood levels. In cases in which depression of blood cholesterol values was observed during

the acute stage of disease, there was rapid return to normal levels during the recovery stage, and even high cholesterol ester levels were observed.

Serial blood cholesterol determinations are of importance in estimating the extent of liver damage; however, they are inferior to blood urea serial determinations since "esterstürz" was absent in two of five fatal cases.

TABLE 3

DAY AFTER ADMISSION	UREA MG. %	T.CH.	F.CH.	CH.E.	F/E	CEPH. T.*
Case IX						
1.	17					+++
2.	14	162(205)†	92(63)	70(140)	1.3(0.45)	+++
3.	8					+++
4.	6					+++++
5.	5.4	128	62	66	0.9	+++++
6.	5.4					+++++
7.	4.6	127	76	51	1.5	+++++
8.	Traces					
9.						
10.		dead				
Case XVII						
1.	21	161	114	47	2.4	+
2.	17.5					+
3.						+
4.	14	152	112	40	2.8	
5.	10					++
6.	4.8	149	100	49	2	+++
7.	7.8					+++
8.	18	111	60	51	1.2	++
9.	20					+
10.						
11.	18.6	245	98	147	0.7	+
14.	24					+
21.	17.5	262	82	180	0.4	+
28.			recovered			

\* T.ch. = total cholesterol; F.ch. = free cholesterol; Ch.E. = cholesterol ester; F/E. = Chol. free-ester ratio; Ceph.T. = Cephalin test.

† In parenthesis normal values in pregnancy are given.

ε Hypoglycemia. Fasting hypoglycemia (the lowest value was 45 mg. per cent) was observed in five patients with severe infectious hepatitis. In two patients definite hyperglycemia and in two others normal blood sugar values were found. There was no evident correlation between the severity of the clinical course and the blood sugar concentration. Hypoglycemia, even when very pronounced, cannot be considered a sign of grave import. On the other hand, hypoglycemia which progressively increases despite massive sugar therapy, should be considered a sign of serious hepatic damage.

For illustrative purposes, serial determinations of blood urea, cholesterol and cephalin test in two cases of group C will be reported, the first with fatal outcome from acute liver

atrophy (case IX), and the second recovered after a very severe clinical course (case XVII, see table 3).

From the above observations in severe cases of infectious hepatitis in pregnancy, it may be possible to differentiate between patients who might develop acute liver atrophy and those in whom the disease will exhibit a milder clinical course. A grave outcome should be feared when in a jaundiced pregnant woman excessive vomiting, pronounced mental instability and subsidence of pains in the liver area are noted, when tachycardia and progressive reduction of the size of the liver are demonstrated, and when progressive decrease of blood urea levels is found in serial determinations.<sup>4</sup> The prognosis seems fatal when the fall of urea blood concentration is associated with high blood values of amino-acids and high non-protein nitrogen. Progressive decrease of total cholesterol and especially cholesterol-ester, as well as progressive fall of the sugar blood concentration despite massive sugar therapy, should also be considered signs of severe hepatic damage.

In the 5 fatal cases of group C premature labor marked the onset of the terminal phase. The uterine contractions were surprisingly painless and labor extraordinarily easy. The placenta was expelled spontaneously and was complete in all five cases. Surprisingly, no immediate post partum bleeding occurred. In two cases, however, severe uterine hemorrhage took place 12 and 48 hours after delivery, when hepatic coma set in. This bleeding was not influenced by massive doses of vitamin K or blood transfusions, and necessitated uterine tamponade. During coma, convulsions similar to those observed in eclampsia were noted in two cases shortly before death.

Post-mortem examinations<sup>5</sup> were performed in 4 of the 5 fatal cases. The pathological findings were characteristic of acute atrophy of the liver. The organ has shrunk to one-half or even one-third of its normal size; widespread, almost universal, destruction of liver parenchyma was found in all cases. However, signs of a beginning regenerative process and new hepatic tissue formation could be recognized.

In the four cases of group C, who recovered, the recovery stage was marked by the reappearance of dulness on percussion of the hepatic area. In all 4 cases normal liver size was regained in one week. Tenderness of the hepatic area seen during the preicteric stage often recurred during convalescence. The recession of tachycardia was also one of the first signs indicating recovery in these 4 patients; the pulse rate which ranged between 100 and 140 per minute during the acute stage, decreased to normal levels, but bradycardia was not noted even at this stage.

<sup>4</sup> From a study by Zondek, B., and Black, R. (23) on estrone clearance in liver disease it appears that the inactivation of estrone is adequate in mild and moderately severe infectious hepatitis in pregnancy, while in extremely severe cases the liver is unable to inactivate estrone completely. Therefore, inadequate estrone inactivation in cases of infectious hepatitis in pregnancy may serve as a sign of poor prognosis (23).

<sup>5</sup> We are indebted to Dr. H. Ungar, from the Pathological Institute of the Hadassah University Hospital, who performed the pathological examinations in these cases.

All 4 patients of this group still exhibited certain minor symptoms (lassitude, nervousness, mental depression, abdominal discomfort) when seen one month after the complete recession of jaundice; in one of them chronic hepatitis developed.

#### REMOTE PROGNOSIS OF PATIENTS RECOVERING FROM INFECTIOUS HEPATITIS IN PREGNANCY

In this series of 29 pregnant women with infectious hepatitis six died (one death being related to an obstetrical complication and not to hepatitis), and 23 patients left the hospital in satisfactory condition. The patients were followed for two months to two and a half years after recovery. Twenty-one were perfectly normal and had no subjective complaints or physical findings which could be related to hepatic disease. No laboratory signs of liver damage (cephalin test, Takata-Ara reaction, urinalysis, hippuric acid test, and blood protein and cholesterol) were observed. Three of these 21 women became pregnant again. During their pregnancies no clinical or laboratory signs of hepatic impairment were found; in particular, no manifestations attributed to hepatic dysfunction during pregnancy ("hepatotoxemia of pregnancy"), like persistent fatigue, headache, nausea, vomiting, vertigo etc. were described. In two of these three pregnant women, delivery was normal, while the third was in the seventh month of a normal pregnancy when last seen.

In 2 of the 23 cases, chronic hepatitis set in. Both patients complained of pronounced muscular weakness, frequent headaches, pains and heaviness in the right upper abdominal quadrant; in both, the liver was slightly enlarged and tender, and the sclerae had a subicteric tint. The icterus index, van den Bergh reaction, cephalin test and blood values of glucose, urea, protein and cholesterol were normal; on the other hand, impairment of the liver function could be demonstrated in both these patients by: a) Takata-Ara reaction in both cases was definitely positive; b) hippuric acid synthesis was seriously impaired, since its excretion two hours after intravenous injection of 1.77 g. of sodium benzoate, was respectively 0.57 and 0.44 hippuric acid (normal 0.7); c) urinalysis showed significantly high amounts of urobilin and urobilinogen in both cases.

#### THE EFFECT OF INFECTIOUS HEPATITIS ON THE COURSE OF PREGNANCY, LABOR, PUERPERIUM AND ON THE CONDITION OF THE FETUS

a) *Toxemia of pregnancy.* It has been assumed that liver damage may adversely influence the course of pregnancy and induce various obstetrical complications, and many authors believed that liver damage was a possible etiologic factor of toxemia of pregnancy and eclampsia (24). It might have been expected that in our cases of serious and even fatal liver damage, signs of toxemia of pregnancy would be observed. In none of these patients, however, was hypertension found. Slight albuminuria occurred in seven cases, but this should be related to renal changes of infectious hepatitis which occurs with equal frequency in men (8). Edema of the legs, which was observed in 58 per cent of our patients was related

to hypoproteinemia and cannot be interpreted as a manifestation of toxemia. Furthermore, convulsions simulating eclampsia were observed in two of our patients only during hepatic coma shortly before death; in both these cases other manifestations of eclampsia such as hypertension and albuminuria were lacking and autopsy revealed the typical changes of acute liver atrophy and not those of eclampsia. Convulsions, however, occur in hepatic coma in men as well as in non-pregnant women.

b) *Hemorrhagic complications.* Liver diseases are known to give rise to various hemorrhagic complications such as epistaxis, oral, rectal and uterine bleeding, purpura, etc. Surprisingly, no case of vaginal bleeding occurred in our patients; moreover, no significant hemorrhage occurred immediately after delivery and expulsion of the placenta. As mentioned above, two cases of uterine hemorrhage which occurred 12 and 24 hours after delivery, when hepatic coma set in, were treated by uterine tamponade. Thus, obstetric hemorrhage in our cases occurred as the terminal stage of complete liver failure.

The prothrombin time was recorded in all 29 cases of infectious hepatitis in pregnancy. No significant prolongation was found in any of these patients during the icteric stage of the disease. In two women, who died from acute liver atrophy, definite increase of the prothrombin time was observed shortly before death. In these two cases, therapy with large amounts of vitamin K failed to reduce the prothrombin time.

c) *Premature delivery.* Premature labor was observed in 7 of our patients, (twice in seventh month, three times in eighth month, and twice at the beginning of ninth month). Six of the seven women in whom premature delivery occurred, belonged to group C (severe cases of infective hepatitis), while the seventh patient delivered in the seventh month of pregnancy during the recovery stage from mild hepatitis. In 5 patients premature delivery took place shortly before hepatic coma and was followed by death in a few days; the sixth patient of group C, although somnolent and precomatose during the premature delivery was saved and recovered after a very stormy course.

It seems reasonable to conclude from our experience that the disease, when mild or moderately severe, does not induce premature delivery or abortion (the seventh case of premature delivery in the recovery stage of mild hepatitis could not have been caused by the disease) while hepatitis in its severe form frequently causes premature spontaneous termination of pregnancy. The abortive action of infectious hepatitis in its extremely severe form may be explained either through the influence of liver failure or through the debilitating influence of the disease on pregnancy. In fact, it has been shown (25) that extreme liver damage in animals is able to induce abortion. The extirpation of one-third of the liver does not prevent the normal course of pregnancy while the excision of one-half or more was followed by immediate termination of pregnancy. On the other hand, other infectious debilitating diseases like influenza in its epidemic form, has a high mortality rate in pregnant women and death is frequently preceded by spontaneous abortion or premature delivery (26).

d) *Labor.* Thirteen women delivered during the course of the disease. Pre-



cipitated labor was observed in 5 cases. In 6 patients with a severe form of hepatitis the uterine contractions were exceptionally painless, and the course of labor unexpectedly easy. Except for one case of uterine rupture, no obstetric complications occurred and in no case was there need for any obstetric intervention during labor. In all 13 patients labor seemed to proceed more quickly, throughout all its stages, than in normal women.

e) *Post-partum period.* There was no increased susceptibility to puerperal infection and no puerperal morbidity was observed in 11 patients who delivered during the course of infectious jaundice. A definite relation, however, has been observed between the infectious hepatitis and lactation. In all eight patients who delivered during the course of the disease, as well as in other three women who delivered 2 to 4 weeks after recovery, there was hypogalactia or agalactia. This observation seems significant, since five of these women had abundant milk secretion following previous deliveries.

f) *The influence of infectious hepatitis on the fetus in utero and on the new born.* Evidence exists, both clinical and experimental, that certain viruses can pass from the maternal circulation through the placenta, and infect the fetus in utero. This is the case in vaccinia, chicken-pox, measles and many other virus diseases. On the other hand, in certain virus diseases like anterior poliomyelitis, the fetus in utero never contracts the disease of the mother. The question arises whether the virus of infectious hepatitis is able to invade the fetus and infect it during its intrauterine life. All the new-born delivered at term, following maternal infectious jaundice in different months of pregnancy, or born during the course of the disease, were perfectly normal at birth and did not develop infectious hepatitis. In two cases delivery occurred at the beginning of the ninth month of pregnancy shortly before hepatic coma and death; in both, the infants, though slightly premature, were normal. In five other cases premature delivery occurred at the seventh and the eighth month. One of these premature infants developed normally although weighing only 1900 gm. at birth; four others died during the first week and autopsies in three of them failed to reveal any sign of hepatic disease.

The placentas from all patients who delivered at term were normal in weight, size and histologic structure.

It appears from the above observations, that the virus of infectious hepatitis is not able to infect the fetus in utero, either because it does not pass the chorionic barrier or because it circulates in insufficient amount in the blood to induce infection.

#### FACTORS CONTRIBUTING TO THE PARTICULARLY SEVERE COURSE OF INFECTIOUS HEPATITIS IN PREGNANT WOMEN

Since infectious jaundice occurring during pregnancy frequently takes a much more severe course than in children, men, or non-pregnant women, pregnancy must therefore be considered a decisive factor aggravating the course of the disease. We believe, however, that other factors are also involved. Under-

nutrition, due to insufficient dietary intake or to excessive vomiting seems to play a particularly important role as an additional aggravating factor (table 4).

a) *The role of pregnancy.* Pregnancy is able to aggravate infectious hepatitis and may lead to acute atrophy of the liver, as has been reported by various authors (13 and 22) prior to this study. We found that there is a tendency to a

TABLE 4  
*Factors leading to acute atrophy of the liver in infectious hepatitis in pregnancy*

	GROUP A	GROUP B	GROUP C	DEAD
1. Period of pregnancy.....				
First half		5	1	
Second half	2	9	8	6*
Post-partum period		4		
2. Epidemic factor				
January, February, March	1	5		1*
April, May, June		4		
July, August, September		5	2	
October, November, December	1	4	7	5
3. Undernutrition				
Undernourished		4	9	5
Well-nourished.....	2	14		1*
4. Vomiting				
Excessive		6	9	6*
Not excessive	2	12		
5. Chronic diseases				
Amebic dysentery		4		
6. Age				
20-25 years		5	4	2
26-30 years	1	6	3	2
31-35 years	1	5	2	2*
36-40 years		2		

\* This patient died following uterine rupture during delivery; the autopsy showed fulminant internal hemorrhage and typical signs of infectious hepatitis (no acute liver atrophy!).

more severe jaundice in cases in which pregnancy is farther advanced, since all five fatal cases of acute liver atrophy occurred during the last trimester of pregnancy.

b) *Undernutrition.* All the patients with the severe form of the disease (group C) were seriously undernourished. The daily intake of these women was particularly low in protein and in various factors of the vitamin B complex. All these patients showed, on admission, distinct symptoms of riboflavin or nicotinic acid deficiency (glossitis, angular stomatitis and in 4 cases pellagroid

changes of the skin). In general, it may be said, that the average daily protein intake (30-40 gm.) of these seriously ill patients never exceeded a third of the minimal protein requirements during pregnancy (85-125 gm. daily) (27).

Evidence is available that deficiency in these fundamental nutritional factors may promote or at least favor liver injury in man (22). The deleterious effects of malnutrition played, in our opinion, an important role in the conversion of simple hepatitis into acute liver atrophy (table 4).

c) *Excessive vomiting.* Excessive vomiting in the early phases of infectious hepatitis, particularly frequent in pregnant women, may lead to starvation due to inability to retain ingested food. The role of starvation in promoting liver damage is generally admitted (22). Excessive vomiting was observed in 15 of our 29 patients (nine of group C and six of group B) (table 6).

d) *Epidemic factor.* We observed that all five fatal cases from liver necrosis and the majority of severe cases of infectious hepatitis in our patients occurred at the beginning of the cold season in this country (October, November and December) (table 4). It has been noted that this seasonal increase in the severity of the infectious jaundice in pregnancy is synonymous with the general increase in frequency of this disease among the population as a whole (17). It seems possible that the virus acquires an increased virulence through multiple transitions from one person to another during epidemics; this may lead to fatalities when the hepatotropic virus attacks pregnant women in whom the liver is particularly susceptible to injurious agents. On the other hand, other infectious disease in epidemic outbreaks carry a definitely higher mortality rate in pregnant women than in the general population. In fact, the widespread pandemic of influenza in 1918 was extremely disastrous in pregnant women, and caused a mortality rate of 25 per cent (26).

e) *Other factors.* We did not find any chronic diseases or intoxications able to cause liver injury in the past history of our patients, except for 4 cases of chronic amebic dysentery observed in patients with a relatively mild hepatitis (group B) (table 4). No significant relation could be found between the age of our patients and the severity of infectious jaundice (table 4).

#### THERAPY OF INFECTIOUS HEPATITIS IN PREGNANCY

a) *General treatment.* The therapy of infectious hepatitis occurring in children, men and non-pregnant women does not represent a major problem. Much more attention should be attached to the therapy of infectious hepatitis in pregnant women, owing to its severe course and high mortality rate.

The liver is endowed with great regenerative powers and exhibits a tendency to heal spontaneously if the action of the injurious agent is arrested and the necessary essential dietary factors are administered (29). It has been shown that in rats the removal of 70 per cent of the liver is followed by its complete regeneration in 7 days if a well-balanced diet is maintained (30).

This particular regenerative capacity of the liver gives, in our experience, full justification to expect possible recovery even in most serious cases of liver damage. Since this regenerative process is promoted by essential nutritional factors, these

latter should be given freely in the treatment of infectious hepatitis in pregnancy. Carbohydrates, proteins, essential amino-acids and vitamins are essential for the protection against liver injury or for the healing of an existing liver damage.

*Carbohydrates* were incorporated in the daily diet (400 gm.) in cases of group A and B or given, mostly intravenously, in cases of group C, owing to the continuous nausea and excessive vomiting (twice daily 500 cc. of 50 per cent glucose sol. = 250 gm. glucose). In cases in which oral intake was possible, 250 gm. of glucose powder were given daily, mixed with milk or lemonade (table 5).

TABLE 5  
*Scheme of treatment in cases of infectious hepatitis in pregnancy*

Groups A and B (mild and moderate cases)		
Carbohydrates	orally	400 g. daily (in the diet).
	intravenously	25 g. in 100 cc. of 25% glucose solution
Proteins	orally	100-120 g. daily (in the diet)
	intravenously	occasionally: 300 cc. blood (cases with anemia) occasionally: 300 cc. plasma (cases with hypoproteinemia)
Amino-acids	orally	protein hydrolysates—25.0 daily
Vitamins	orally	yeast (variable doses), thiamin 20 mg., nicotinic acid 200 mg., riboflavin 15 mg., vitamin C 400 mg., vitamin K 10 mg.
Group C (severe cases)		
Carbohydrates	orally	250 g. or more daily (in the daily diet)
	intravenously	250 g. in 1000 cc. of 25% glucose sol
Proteins	orally	80-120 g. daily (in the daily diet)
	intravenously	blood 300-500 cc. daily (appr. 11.5-18.0 nutritional proteins) plasma 300-600 cc. daily. (18.0-36.0 g. proteins)
Amino-acids	orally	protein hydrolysates 25-50 g. daily (in the diet)
	subcutaneously	methionin 3.0 g. daily (2 cases only)
Vitamins	intravenously	thiamin 20 mg., Riboflavin 10 mg., Vitamin C 400 mg.
	subcutaneously	nicotinic acid 150 mg.
	intramuscularly	vitamin K 10 mg.

*Proteins* were administered in the daily diet (100 gm. at least), the major part of which were given in the form of milk (1.5-2 liters daily) and cheese (100-150 gm. daily). Parenteral protein therapy consisted in intravenous administration of whole blood and plasma. The whole blood transfusions exerted an additional benefit by red cell replacement, since in the severe form of hepatitis anemia was commonly found. In cases of groups A and B the protein requirement was covered chiefly by oral administration and only occasionally blood transfusion (if anemia was present) and plasma transfusion (in cases with pronounced hypoproteinemia) were necessary (table 5). In cases of group C, transfusions of 300-500 cc. of whole blood and 300-600 cc. of plasma were given daily during periods

extending from 3 to 7 days, until the clinical and laboratory findings showed that the destructive process of liver tissue was arrested (increase of liver size, rise in urea blood level, etc.).

*The essential amino-acid* daily intake was raised by the administration of protein hydrolysates (Aminoids Arlington). Methionin has recently been claimed to be the specific amino-acid in the prevention of liver damage (31). It was given in only two severe cases in this series (3.0 gm. daily subcutaneously) and in both cases acute atrophy of the liver could not be avoided. It should be remarked that our experience with this substance is insufficient and the doses employed were too small to permit definite conclusions. (Methionin was not available in sufficient amounts in this country during the war.)

*Low-fat diet.* Fatty food stuffs were avoided in all our patients since proof is available that food rich in fat produces maximal susceptibility to liver injury (32).

b) *Obstetrical treatment.* Certain precautions are advisable during the delivery in patients with infectious hepatitis. Operative interventions should be avoided as far as possible, since hemorrhage may occasionally occur from operative wounds.<sup>6</sup> General anesthesia should be prohibited because injury of the liver has been observed not only following administration of chloroform but also (although less pronounced) with nitrous oxide and ether (33); when intervention is necessary, the anesthesia of choice is local infiltration with novocain.

The outstanding problem in the obstetrical treatment of infectious hepatitis in pregnancy is whether artificial interruption of pregnancy should be performed. On this problem the data available in the literature are very confused. In general, no special attention is attached to infectious jaundice (formerly called "catarrhal jaundice") in pregnancy. This is considered a rare and benign condition which does not need special obstetrical treatment. On the other hand, the almost unanimous opinion is that the uterus should be emptied as rapidly as possible when jaundice appears as a manifestation of acute atrophy of the liver (15, 20, 34 and 35). In spite of this therapy, however, the almost constant fatal outcome of acute liver atrophy in pregnancy is emphasized. The following reasons may be given in favor of interruption of pregnancy in severe cases of infectious hepatitis: 1) the course of the disease is undoubtedly aggravated by pregnancy, 2) acute liver atrophy is more frequently seen in pregnant women than in children, men, or non-pregnant women, and 3) pregnancy exerts an unfavorable influence on liver function.

In our opinion, however, based upon the results of this study, an active attitude in these cases is not advisable. The "catarrhal jaundice" in pregnant women is a form of infectious hepatitis which may occur in sporadic, endemic or epidemic form. This disease may sometimes assume a completely benign or even sub-clinical course or, on the contrary, may manifest itself by the fatal clinical picture of acute liver atrophy. The artificial termination of pregnancy, when performed at the onset of liver atrophy may aggravate liver damage. If, however, the interruption of pregnancy is performed at the onset of the disease, one may be sacrificing the fetus in a case which may have had a benign clinical course. Fur-

<sup>6</sup> In our series hemorrhage occurred in only two cases before death.



thermore, such intervention may not only be without benefit to the mother, but may greatly aggravate the hepatitis by the trauma which it involves. In fact, evidence is available that impairment of liver function and even acute liver necrosis may follow any surgical intervention in patients with liver damage (22).

In our opinion, infectious hepatitis in pregnant women should be considered, above all, as an infectious disease complicating pregnancy. The general rules in the management of infectious diseases occurring during pregnancy, are applicable also to infectious hepatitis. It is well known that pregnancy exerts a definitely adverse effect on the course of most infectious diseases, e.g. typhoid fever (37), pneumonia (38), influenza (26), smallpox, measles and epidemic lethargic encephalitis (39). Nonetheless no one considers it advisable to interrupt pregnancy in pneumonia, even if the course of the disease is very severe. Certain epidemics of influenza in pregnant women exhibit a very similar clinical course to the one observed in infectious hepatitis: actually, in very severe cases of influenza, spontaneous abortion or premature delivery frequently occurred shortly before death of the patient. In these cases the conclusion was reached that artificial interruption of pregnancy may aggravate the course of the disease and should be strongly discouraged (40). The above also applies to infectious hepatitis in which, according to our experience, the aggravation of the clinical course after spontaneous abortion or delivery point strongly against the artificial interruption of pregnancy.

In our series of infectious hepatitis in pregnancy, five women died from acute liver atrophy which set in shortly after spontaneous premature delivery. In all cases the disease became definitely aggravated by the termination of pregnancy. Of the other severe cases (of group C) the artificial interruption of pregnancy was performed in two (by curettage in one case and by artificial rupture of membranes followed by introduction of uterine metreurynter in the second case), while in two other patients the pregnancy was permitted to continue its normal course. All these 4 women recovered. However, the artificial interruption of pregnancy was followed in both patients by a temporary aggravation of the patient's condition manifested by a further decrease of the liver size, drop in blood urea values in one case and decrease of the cholesterol ester level in another. These observations led us to abandon the interruption of pregnancy in infectious hepatitis. Consequently, in our judgement, artificial termination of pregnancy should be discouraged in infectious hepatitis in pregnant women in the interest of both mother and fetus.

c) *Results of treatment in infectious hepatitis in pregnancy.* Despite treatment 5 patients died from acute atrophy of the liver (17.2 per cent), and one patient died from accidental intra-peritoneal hemorrhage due to uterine rupture at delivery. It should be emphasized that, although this mortality rate is high, four pregnant women presenting symptoms of extremely grave prognostic omen (as comatose condition, tachycardia, fetor hepaticus, progressive reduction of liver size and laboratory findings of very severe liver damage) could be saved. These results seem to us not bad, since in another epidemic (13), observed in Istanbul 13 out of 14 (92 per cent) pregnant women died from acute atrophy of the

liver. Chronic hepatitis with clinical and laboratory findings of liver impairment was observed in two patients (7 per cent), two and one and one half years after recovery from acute hepatitis in pregnancy. Twenty-one patients were found completely recovered when examined three to six months after delivery; three of them became pregnant again and had uneventful pregnancies.

#### COMMENT

Catarrhal jaundice in pregnancy is generally described as a benign disease; on the other hand, a number of epidemics of jaundice in pregnancy with a very high mortality (92 per cent) have been reported (13). These two forms of jaundice have been considered as two different diseases until recently, when it was established that both are due to the same icterogenic virus of infectious hepatitis. In the light of this discovery the benign "icterus catarrhalis" and the extremely serious epidemic jaundice in pregnant women should, in our opinion, now be considered as the same disease.

The early diagnosis of the disease and intensive treatment from its very inception seems of great importance. Unfortunately, the diagnosis is particularly difficult in the early, preicteric stage. One must be particularly cautious in the diagnosis of infectious hepatitis in pregnant women, since general symptoms characteristic of the preicteric stage, e.g. anorexia, nausea and vomiting, may be induced by pregnancy without hepatic involvement. The routine urinalysis for bilirubin in all pregnant women at times of epidemics is very helpful. Following its introduction in our Centres of Prenatal Care, two cases of hepatitis without jaundice and two others in the preicteric stage were detected. The diagnosis of infectious hepatitis may become very difficult, if jaundice develops during the pernicious vomiting of pregnancy.

In the diagnosis of infectious hepatitis the possibility of spirochetal jaundice (Weil's disease) should be considered. It is noteworthy that during epidemics of infectious hepatitis there may be concomitant epidemics of spirochetal jaundice.

In this study of 29 pregnant women with infectious hepatitis the symptoms which indicate the danger of acute atrophy of the liver before hepatic coma sets in are described. The finding of a progressive decrease of the urea blood level is a most valuable sign of the severity of the disease and has been found in all our five fatal cases as well as in three other very severe instances. It might seem surprising that the depression of urea synthesis, considered a most essential and less vulnerable hepatic function, figures as our most important laboratory sign of the severity of infectious hepatitis in pregnancy. In fact, it has been found in animal experiments that four fifths of the liver may be removed without a significant effect on urea synthesis (41). Furthermore, liver damage frequently induces a rise of the blood urea level, and only in exceptional cases is a decided lowering of the urea level observed. However, we found in our cases a sudden drop in the blood urea value may occur before clinical signs of aggravation of the disease appear. In all our five fatal cases lowering of blood urea level preceded by several days the appearance of hepatic coma. This observation leads us to the conclusion that a progressive decrease of the urea blood level is a more useful

indication of the severity of infectious hepatitis in pregnancy than any other liver function test. Furthermore, inadequate estrone inactivation (positive estrone clearance test) may serve as a sign of poor prognosis. The intensity of the icteric tint is not an important sign pointing to the severity of infectious hepatitis. In fact, no relationship could be found between the severity of the clinical course and the depth of the jaundice. Numerous cases of intense jaundice with an icterus index of 300 and without particularly serious hepatic functional impairment were observed. On the other hand, four of five patients who died from acute atrophy of the liver presented deep icterus (icterus index 300 at its peak value), while in the fifth case jaundice was never particularly deep (icterus index 100 at its peak value). It seems also surprising that although hemorrhages frequently appear in serious liver diseases, they have not occurred in our patients, except in two cases shortly before death. Furthermore, the prothrombin time, considered a sensitive test of liver damage, was normal in all our cases during the icteric stage, and became prolonged only in the two above mentioned cases in hepatic coma.

In the study of the factors leading to acute liver atrophy in pregnant women with infectious hepatitis, special attention has been attached to the role of under-nutrition. It seems that undernourished pregnant women with a daily intake especially low in proteins, are particularly apt to develop acute atrophy of the liver as a complication of infectious hepatitis. Consequently, a well balanced diet, rich in proteins is to be recommended to all pregnant women living in areas of epidemics of infectious hepatitis. The therapy in severe cases consists chiefly of intravenously administered protein and glucose. We frequently used blood transfusions successfully in these cases (table V), although the use of whole blood in liver diseases is generally discouraged.

#### SUMMARY AND CONCLUSIONS

1. A clinical study of infectious hepatitis in pregnancy was made in 29 patients observed among 3,382 pregnant women (0.85 per cent) over a period of 32 months, extending from October 1943 until July 1946.

2. It has been shown that infectious hepatitis in pregnancy may assume three different clinical courses and, therefore, our patients have been divided into three groups according to clinical severity.

- A) Hepatitis without jaundice (group A) comprising two (7 per cent) particularly mild cases of infectious hepatitis in which there was no clinically apparent jaundice but with transitory bilirubinuria. In these patients clinical symptoms were mild and laboratory tests showed only slight impairment of liver function.
- B) Moderately severe hepatitis (group B) was observed in 18 pregnant women (62 per cent). The pathologic manifestations exhibited by these patients resembled those observed in infectious hepatitis uncomplicated by pregnancy with, however, the following differences:
  - a. Insidious onset with the symptoms of the preicteric stage often misinterpreted by the patients as due to pregnancy.

- b. Frequent occurrence of glossitis and angular stomatitis due to vitamin B deficiency.
  - c. Rare incidence of itching and bradycardia.
  - d. Serious functional impairment of the liver demonstrated by hypoproteinemia, positive cephalin and Takata-Ara tests, decrease of the total and cholesterol-ester blood levels and fasting hypoglycemia.
- C) Severe hepatitis with a tendency to acute atrophy of the liver (group C') was observed in 9 cases (31 per cent). The frequency of this severe form of hepatitis in pregnant women is emphasized and the following manifestations are stressed as indicative of the severity of the disease:
- a. General symptoms: excessive vomiting, pronounced mental instability and subsidence of pain in the liver area.
  - b. Physical findings: tachycardia and progressive reduction of the liver size.
  - c. Laboratory findings: progressive decrease of the urea blood levels found at serial examinations, rapidly decreasing total cholesterol and cholesterol-ester blood values, persistent hypoglycemia and inadequate estrone inactivation (positive estrone clearance test). Five patients of this group died from acute atrophy of the liver.
3. The remote prognosis of patients recovered from infectious hepatitis in pregnancy was studied with following results:
- a. In 2 patients (7 per cent) chronic hepatitis resulted from infectious jaundice during pregnancy.
  - b. Twenty-one patients showed no signs of liver function impairment when examined 3 to 6 months after recovery.
  - c. No functional hepatic impairment was found in 3 women, who became pregnant again.
4. Investigation of the effect of infectious hepatitis on the course of pregnancy, labor, puerperium and on the condition of the fetus leads to the following conclusions:
- a. Hemorrhage was exceptionally rare and observed in only 2 cases shortly before death.
  - b. Premature deliveries are frequent in the severe form of hepatitis.
  - c. Labor proceeded rapidly throughout all the stages.
  - d. Agalactia and hypogalactia are common in women who delivered during the course or shortly after recovery from infectious hepatitis.
  - e. The fetus was never affected by the disease of the jaundiced mother.
5. The following factors contributing to the particularly severe course of infectious hepatitis in pregnancy have been suggested:
- a. Pregnancy is the decisive factor contributing to the severity of infectious hepatitis.
  - b. Stage of pregnancy: all 5 fatal cases and the majority of severe cases of infectious hepatitis were observed during the late second half of pregnancy.
  - c. Undernutrition: all our patients who exhibited the severe form of the disease were undernourished, their daily diet being particularly low in proteins and in the various factors of vitamin B complex.

- d. Excessive vomiting interfering with food intake.
- e. Epidemic factor: all 5 fatal cases and the majority of severe cases were observed at the time of the general increase of the disease among the general population.
6. Treatment consisted in the administration of fundamental nutritional factors (carbohydrates, proteins, essential amino-acids and vitamins) in high doses; parenteral administration of nutrients was used in patients suffering from excessive vomiting. Blood transfusions were frequently administered.
7. The problem of therapeutic interruption of pregnancy is discussed and the conclusion is reached that it should be discouraged in the interest of both mother and fetus.
8. The final outcome in this series of infectious hepatitis in 29 pregnant women was as follows: Five patients died from acute atrophy of the liver (17.2 per cent). One patient died from accidental intraperitoneal hemorrhage due to uterine rupture at time of delivery. In 2 patients the disease was followed by chronic hepatitis (7 per cent). Twenty-one patients recovered completely (72 per cent).

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## FULL-TERM PREGNANCY FOLLOWING OPERATION FOR ATRESIA OF THE VAGINA\*

JOSEPH L. BAER, M.D.

(Chicago, Illinois)

Anomalies of the genital tract can occur at one or more points throughout its extent. It is accepted that they are due to an inadequate or misdirected vis a tergo of the mesonephros and/or the Mullerian ducts. The primary etiology can reside in defective maternal or paternal germ plasm or in disorders of very early pregnancy. Some of these anomalies result in primary sterility. This includes the group in which there is non-union of the Mullerian system with the ectodermal vaginal inpouching.

These young patients usually seek medical advice because of a long standing primary amenorrhea. The imperforate hymen is the simplest of the defects encountered in this group. Dissection is a cure and pregnancy can eventually occur if there are no other handicaps.

More or less complete absence of the vagina, even in the presence of a functioning uterus, as evidenced by hematometra, is not unusual. A connection can always be established surgically. Usually coitus can be made possible and maintained. However, where major dissection has been necessary, the subsequent occurrence of pregnancy is a rarity. In fact only two reports of such an event have been found in the literature.

Whittemore (1) reported the case of a 21 year old white female who developed regularly recurring (every eight weeks) severe cramp-like abdominal pain at the age of 15. She married at 18 and one and a half years later, for the first time, began to bleed regularly from the urethra every 8 weeks; the flow lasting three to four days. Marital relations were impossible. At operation a cavity between the rectum and the bladder was created and lined with prepared skin flaps from the thigh and labia minora. The thigh flaps necrosed but the labial flaps grew and rapidly epithelialized the canal. She became pregnant shortly after the operation and was delivered at term, by cesarean section, of a normal baby weighing five pounds, 9 ounces. At operation, absence of the left adnexa, round ligament, broad ligament and left uterosacral ligament as well as left kidney was observed—a true uterus unicornis.

Wagner (2) reported the case of a 27 year old white female who had severe dysmenorrhea since 15, associated with a trickle of blood at regular monthly intervals. Examination revealed a tiny canal connecting a normal uterus with a 2 cm. vaginal pouch. Coitus was impossible. The tract was excised and a segment of sigmoid was used to join uterus and vaginal pouch (Schubert technic). Conception followed within eight months. Cesarean section was planned but the patient was delivered at term by forceps and episiotomy. The baby was normal, weighing 2750 gms. Four years later Wagner (3) reported that the patient had two subsequent children, the last weighing 4500 gms.

### CASE REPORT

This is a report of a third instance of pregnancy subsequent to surgery for absence of the vagina, but it differs from the preceding case reports because this patient was completely amenorrheic until surgery.

\* From the Department of Obstetrics and Gynecology, Michael Reese Hospital.

The history of our patient, Mrs. E. K., (Miss E. M.) begins with her birth on December 5, 1920. She was the second of identical twins, and weighed 5 pounds, 8 ounces, four ounces less than her sister. No abnormalities were observed in either child.

The surgical procedure was carried out on October 16, 1937 and was reported to the Chicago Gynecological Society, December 17, 1937. That report follows:

"This case report deals with a complete atresia of the upper two-thirds of the vagina, i.e., that portion of the vaginal tube which arises from the fusion of the lowermost parts of the Müllerian bodies.

"The patient, E. M., aged 16 years, had never menstruated. Her identical twin sister had menstruated more or less normally for approximately two years. The girl was seen



FIG. 1. Pelvic x-ray after transabdominal pneumoperitoneum revealing uterus and adnexae

by the school physician who found a mass in the abdomen. She was then brought to me. On examination the external genitalia were normal. It was possible to insert the first phalanx past the intact hymen into a closed pouch, the depth of which was no greater than 2 cm. On rectoabdominal examination the mass which the school physician had felt was about the size of a four months' pregnancy, with something of the outline of the uterus, freely movable, insensitive and with a tapering lower pole. An intravenous pyelogram was made to make sure there was no anomaly of the urinary system, and then after transabdominal pneumoperitoneum pelvic x-ray was made (fig. 1), in order to determine the amount of tissue that lay between the lower pole of the mass and the apex of the exceedingly small vaginal tube. The approximate distance between this tiny vaginal vault and the lowermost pole of the uterine mass was 6 cm. (fig. 2). Evidently only the ectodermal invagination had taken place. The denser shadow within the uterine mass was interpreted as retained menstrual blood.

"There are two surgical approaches to this problem, one, vaginal the other abdominal. In the literature two points are emphasized; first, that if possible, where there is functioning endometrium it is desirable to establish menstruation by connecting the blind lower uterine pole with the vaginal pouch; second, in the adolescent girl it is highly desirable to do nothing more, but to await marriage. If the tiny vaginal tube remains inadequate for coitus and it becomes necessary to do a vaginal plastic operation, then marital coitus is essential to the permanent success of the plastic operation. In this instance the vaginal approach was selected.

"Under ethylene-oxygen anesthesia the apex of this tiny vaginal vault was split transversely, and then with a sound in the urethra and bladder and the assistant's finger in the



Fig. 2. Pelvic x-ray with visualization of hypoplastic vaginal pouch distended by opaque medium. Note the distance between the vaginal vault and the uterine mass

rectum, we proceeded with blunt and sharp dissection through the rectovaginal tissue. Meanwhile abdominal pressure was made to bring the lower pole of the mass somewhat closer to the vaginal pouch. Eventually it was possible to grasp the lower pole with a tenaculum, and then with a little further blunt dissection a single droplet of black, thick fluid appeared, obviously some retained menstrual blood. With sound exploration a canal was identified and dilated. Approximately 10 to 12 ounces of retained black menstrual blood escaped. The so-called cervix was then brought down to the level of the little vaginal vault where it was anchored with mattress sutures. The girl made an uneventful convalescence. The date of the operation was October 16 and last week, December 10, she had her first normal menstrual period.

"The abdominal approach in these patients is distinctly unsatisfactory. The depth of the cul-de-sac and the dissection necessary to reach such a tiny vaginal pouch from above is obviously more difficult than the approach from below. However, if the all-important preliminary intravenous pyelogram reveals possible involvement of one or both ureters in the anomalous development, then the abdominal approach becomes the safer route."

Examination in April, 1939, eighteen months after surgery, disclosed a vagina 5 cm. long with the lower pole of the uterus flush with the top of the vaginal vault. No vaginal cervix existed. Menses were regular every 26-27 days, lasting 4 to 5 days and associated with little discomfort.

In October, 1941 the patient married. With the release of her husband from military service, contraception was discontinued and pregnancy followed within one month. Examination when the patient was ten weeks pregnant revealed vaginal status identical with that of 1939. The corpus was normally enlarged and anteflexed. In the region of the right cornu there was a firm pedunculated mass 3 cm. in diameter. All laboratory studies were normal although the patient was Rh negative and her husband was Rh positive. She weighed 121 pounds.

Pregnancy progressed uneventfully until the seventh month when she suddenly developed pain and tenderness in the right upper quadrant. Tenderness became localized to the region of the pedunculated mass previously noted. After a few days of bed rest, most of the discomfort subsided although the mass remained slightly tender throughout the rest of the pregnancy.

Doctor Edwin J. DeCosta, one of my partners who was taking care of this patient discussed the contemplated mode of delivery with me. Since there was neither a detectable cervix, nor even a detectable orifice into the vaginal vault at term, elective cesarean section was decided upon.

Under cyclopropane-oxygen she was delivered of a normal 7 pound 15 ounce male by laparotrachelotomy on July 27, 1946. At operation a well formed lower uterine segment was found. After the contents of the uterus had been evacuated and the bleeding well controlled, search was made for a cervical canal. It was considered vital to make sure of a free outlet for the lochia. A no. 10 Hegar dilator readily passed through a canal in which there was a bit of inspissated mucus. The abdominal organs were carefully examined. A degenerated pedunculated myofibroma was found in the region of attachment of the right round ligament; this was removed.

One striking abnormality was found. The ovarian arteries along the infundibulo-pelvic ligaments were entirely superficial, coursing just under the peritoneum along the superior border of the ligaments and were exceedingly tortuous. There were no other abnormalities. Her postoperative convalescence was uneventful and she went home on the tenth day.

*Comment.* The simple operative procedure described above served a very useful double purpose, (1) it provided an outlet for menstrual flow and (2) provided a canal for impregnation. Both purposes were successfully achieved.

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## ASPIRIN POISONING IN INFANTS

MURRAY H. BASS, M.D.

(New York, N. Y.)

Since the introduction of the use of massive dosage of salicylates in the treatment of acute rheumatic disease, the incidence of salicylate poisoning has increased, and numerous articles have appeared on the subject (1). Especially the intravenous administration of the drug has led to severe poisoning and even to fatalities, so that many clinicians have discontinued this method of treatment (1d). The wide use of massive dosage and the reports of occasional toxic reactions has thus made the practitioner more conscious of the dangers of the drug. The pediatrician is naturally interested in this subject since so many cases of rheumatic disease occur in children between 5 and 15 years. The occurrence of salicylate poisoning in infants, however, although reported in the literature, is not so well known and it is my purpose here again to call attention to this subject and to point out that it is probably more common than is generally believed and is often unrecognized. During the past two years I have seen three cases of severe salicylate poisoning in infants, one of them fatal. I believe these cases are important because none of them was due to accidental taking of the drug, but in all the dosage had been prescribed by physicians. Since the use of salicylate, especially aspirin, has become so indiscriminate, physicians are apt to forget not only that certain individuals may have an idiosyncrasy for the drug, but that the dosage, even in the average individual, must be definitely controlled. One is so accustomed to giving aspirin without specifying a certain dose, that I found myself warning patients about the danger of the indiscriminate use of the sulfa drugs when they were first introduced by telling them that they must be careful as "these drugs cannot be taken without directions—like aspirin." Particularly then when the patients are infants, the dosage of salicylate must be definitely controlled.

My own interest in salicylic acid poisoning was first aroused by the following case:

*Case 1.* A female infant aged 5 months was the third child of healthy parents. From earliest infancy she had been a feeding problem and various feedings had been tried. She gained very slowly so that at the age of 5 months she weighed only 8 pounds. She had never been actually ill until one day before I saw her when she was said to have developed a "cold" for which aspirin was prescribed. During the night the baby had become more and more restless and breathing had been noted to be deep and rapid. She had had very little fever. The medication was continued throughout the day in the belief that the child had a pulmonary infection. As the infant's general condition got progressively worse, another physician was summoned at 8:00 p.m., about 36 hours after the onset of the illness. He at once realized the gravity of the situation and asked me to see the baby with him. At 9:00 p.m. it was evident that the child was suffering from an overwhelming toxemia. She was cold and clammy and cyanotic. The temperature was subnormal. The pulse could not be felt. There was great hyperpnoea with rapid deep respirations. The eyes were deeply sunken. The skin was dry with loss of normal tissue turgor. The fontanelle

was markedly depressed. As far as could be ascertained, the lungs were normal. The heart beat was very rapid but regular. The throat was congested. The ear drums were normal. The abdomen was soft and the liver edge was felt 2 cm. below the costal margin.

It was evident that the baby was in deep acidosis, greatly dehydrated and moribund. On account of the absence of diarrhoea, it was difficult to explain the picture except on the basis of an overwhelming intoxication. On further questioning it was then ascertained that the infant had received 5 grains of aspirin every 4 hours, a total of 28 grains in the course of  $1\frac{1}{2}$  days.

All the symptoms could be easily explained as the result of this enormous overdosage of salicylate,—more than 10 times the correct amount had been prescribed. The baby was immediately sent to the hospital, but died on the way.

Regardless of the absence of laboratory data and of the underlying infection which may have been present, the symptoms were quite characteristic of salicylate poisoning. In this case the history of the enormous dosage made the diagnosis quite simple. However, there are cases where the individual may have an idiosyncrasy to the drug so that symptoms may appear when doses not so greatly in excess of the normal have been prescribed. The following case is an illustration:

*Case 2.<sup>1</sup>* An 8½ months old previously healthy female infant developed fever and a pharyngitis. Aspirin,  $2\frac{1}{2}$  grains, every 4 hours was prescribed together with several doses of sulfadiazine. For the first day the medication was vomited but on the next it was retained, in all the child received  $12\frac{1}{2}$  grains of aspirin. At 11 p.m. the baby fell asleep and when seen the following morning seemed bright, though the temperature was  $102^{\circ}\text{F}$ . and deep sighing respirations were noted. An alkaline preparation (Citralka) was prescribed and since the baby seemed comfortable, it was left at home. Except for deep, Kussmaul-like respirations, physical examination was negative. At 11 a.m. the infant had a severe prolonged convulsion and appeared very ill. It was hurried to the hospital where it was put into an oxygen tent, a clysis of Hartmann's solution was given, Sodium bromide was given rectally and Sodium luminal hypodermatically. Penicillin was also started, 20,000 units every 3 hours, as the condition was considered an infection. At 2 p.m. the child suddenly collapsed, became pulseless, cyanotic and vomited a large amount of coffee-ground material and appeared moribund. Vitamin K and Coramine were ordered hypodermically and in order to save time, a blood transfusion was given into the tibial marrow. In the meantime a continuous intravenous drip of Hartmann's solution was started.

It was at 6 p.m. after these measures had improved the infant's condition that I first saw it. The baby was still breathing with very deep respirations, was unconscious but the pulse, though rapid, was palpable. There was no clinical evidence of any kind of infection and a radiograph of the chest revealed normal lungs. The urine, except for ++ acetone, was normal. The blood showed hemoglobin, 12 gms.; red blood cells, 4,250,000; platelets, 370,000; white blood cells, 31,000 with 75 per cent lymphocytes.

The child's condition gradually improved, the temperature was normal after 48 hours and remained so, the blood count fell to normal, the acetonuria disappeared and the baby was discharged from the hospital well, three days after admission.

On reviewing the history, it was noted that the child had at first had a very mild upper respiratory infection, that it had received an excessive amount of salicylate and that after a period of apparent well-being all the symptoms of salicylism made their appearance—hyperpnoea, convulsions, collapse, ace-

<sup>1</sup> Data for this case were kindly furnished by Dr. Maurice A. Shinefeld.

tonuria, and hematemesis. Although at the time the etiology of the illness was not known, the symptomatic treatment given was exactly that which is recommended for salicylate poisoning, namely, fluids intravenously, molar lactate solution, oxygen, sedatives and vitamin K.

Unfortunately it was impossible to obtain blood for salicylate level, but the absence of any other etiological factor for the illness, the characteristic symptoms and the response to therapy, I think make the diagnosis certain.

The third case is another example of overdosage in which the symptoms went unrecognized and the baby was treated for otitis and later for pneumonia. It is important to note that fever may be a symptom of salicylate poisoning and that its presence may easily lead to confusion in diagnosis.

*Case 3.<sup>2</sup>* Joseph F. (Hospital Adm. #548844), a 5 month old male infant was admitted to the Mount Sinai Hospital on May 12, 1946. Birth and development were normal. One week before admission the infant had shown signs of a mild respiratory infection, and in spite of apparent subsidence of the respiratory symptoms the temperature rose higher each day until on admission to the hospital it had reached 106°F. There was no diarrhoea.

The baby looked extremely ill and the most striking symptom was the deep and very rapid respiration. There was no grunting respiration nor was there dilatation of the alae nasi. The lips were cyanotic. The patient was extremely irritable. The fontanelle was not bulging. The pupils were equal and slightly dilated. The ocular fundi were negative. The left ear drum was pink, the right was not visualized. The pharynx was normal. The liver edge was palpable 1½ cm. below the costal margin. Otherwise physical examination was negative. The lungs showed no abnormality and a chest radiograph was negative. There were no petechiae nor any evidence of a hemorrhagic tendency.

The hemoglobin was 68 per cent; the white blood cells, 10,000; segmented polymorphonuclear cells 58 per cent; non-segmented polymorphonuclear cells 5 per cent; lymphocytes 35 per cent; monocytes 2 per cent. Blood CO<sub>2</sub> was 36 vol. per cent. Nose and throat cultures revealed staphylococcus albus B, streptococcus viridans and micrococcus catarrhalis. Blood culture was sterile. Spinal tap showed clear fluid under normal pressure, no cells, negative Pandy test, negative culture, sugar 130 mg. per cent. Mantoux tests 1:10,000 and 1:100 were negative.

The baby had been seen by a number of physicians, one of whom had performed a myringotomy which yielded no exudate.

The Resident physician having recently been acquainted with the clinical picture presented by salicylate poisoning inquired into the history more carefully and obtained the data shown in the following table.

<i>Days prior to admission</i>	<i>Temperature</i>	<i>Aspirin Medication</i>
6	99.8	2½ grains × 2 5
5	101.0	2½ grains × 2 5
4	101.6	2½ grains × 3 7½
3	101.0	2½ grains × 4 10
2	103.0	2½ grains × 4 10
1	104.0	2½ grains × 1 2½
		Total..... 40 grs.

As the result of these findings blood was drawn for salicylate level which was found to be 1130 gamma per cc. In addition to penicillin and sulfa which the infant was receiving, molar lactate solution and Ringer's solution intravenously were added and the child was

<sup>2</sup> This case is reported through the courtesy of Dr. Samuel DeLange.

placed in oxygen. Within 36 hours the temperature had come down to normal, the cyanosis and dyspnoea disappeared. The  $\text{CO}_2$  combining power rose to 46 vols. per cent, and 2 days after treatment had been started, the blood salicylate level had dropped to 355 gamma. A few days later the infant was discharged well.

The general manifestations of salicylism are hyperpnoea, nausea and vomiting, tinnitus, fever, ketosis, mental symptoms such as irritability, delirium, dizziness, muscular incoordination, convulsions, restlessness and coma. Cyanosis and circulatory failure, with dehydration may finally end fatally. These are the symptoms due to poisoning; others may be due to idiosyncrasy and are allergic in nature. Among these are urticaria, purpura and a tendency to bleed, perhaps due to hypoprothrombinemia.

Hyperpnoea, now considered the commonest symptom of salicylate poisoning, was formerly thought to be the result of acidosis, but recent studies have shown that "salicylic acidosis is a misnomer." The hyperpnoea is central in origin and the excessive exhalation of  $\text{CO}_2$  starts a chain of chemical disturbances which according to Guest and Rapoport may be described as follows: "with a diminished tension of plasma  $\text{CO}_2$  and a shift of the pH toward alkalosis, the plasma bicarbonate tends to diminish by increased excretion of bicarbonate in the urine, a diminution of sodium in the plasma and/or an increase in the chloride ions of the plasma" (2). When the condition goes on unchecked, dehydration and severe acidosis lead to circulatory failure.

Hartmann's (3) conception of what transpires is this: "At first there is primary hyperventilation because of central stimulation, which leads to a  $\text{CO}_2$  deficit type of alkalosis with alkaline urine and moderate compensatory reduction of blood bicarbonate. Then ketosis develops (in one instance also with hypoglycemia) and produces a real bicarbonate deficit acidosis, with a shift to acid urine. Acidemia (reduction of blood pH) may or may not result, depending upon the degree of hyperventilation and whether or not respiratory failure ensues. Ketosis cannot be immediately abolished by administration of glucose or glucose with insulin (the latter to be used with caution because of the tendency toward spontaneous hypoglycemia) and may persist for as long as four or five days, and requires "neutralization" with repeated injections of Na-lactate or sodium bicarbonate, the former preferred because of its glycogenic properties, its greater safety and ease of administration. After ketosis is finally abolished, salicylates may still be found in the body fluids and there may still remain hyperpnoea from central action with a shift again of the acid-base balance to that of  $\text{CO}_2$  deficit alkalosis, requiring  $\text{CO}_2$  inhalation (usually with oxygen) to prevent alkalemia. In fatal cases circulatory and respiratory failure develop."

The nausea and vomiting is also central in origin and is not due to gastric irritation caused by the local action of the drug. Caravati and Whims (4) point out that when salicylates are given intravenously the nausea and vomiting may be even more severe than when administered orally. Moreover they have shown that in cases where intravenous therapy was being given, and the salicylate blood level was at its height, frequent analyses failed to show even a trace of salicylate in the gastric contents. In their cases gastroscopy failed to show

any abnormality of the mucus membrane. The same findings are reported by Paul (5). However the occasional report of hematemesis as one of the symptoms seen in salicylism cannot be disregarded. It would seem likely that bleeding from the gastric mucosa may, as was mentioned above, be a symptom of hypersensitiveness to the drug. Prickman and Buchstein (6) in a report of 62 cases of hypersensitiveness to acetylsalicylic acid consider this the most commonly encountered drug sensitivity. They report cases where purpura resulted from minute doses of aspirin and warn against the use of this drug in asthmatic patients.

That salicylates may cause gastric bleeding is shown by a case report of Hurst and Lintott (7) where unexplained hematemesis was traced to aspirin. In this patient, broken up aspirin tablets were administered and immediately followed by gastroscopy. Congestion of the mucosa was seen with the exudation of blood where the pieces of the tablet lay against the mucus membrane, in fact while being observed the aspirin was seen to be stained pink from the blood.

The conception that this hemorrhagic tendency may be due to hypersensitivity is born out by the history of my second case where very severe symptoms, including hematemesis, resulted though the total drug dosage was only about double the correct amount. A number of papers (8) have appeared warning against the current use of aspirin as a routine before tonsillectomy, as it may predispose to hemorrhage. There is also a possibility that some of the epistaxes seen in rheumatic fever may be due to the drug rather than to the disease. The bleeding may in part be due to hypoprothrombinemia (9) though as Coombs and his co-workers (10) have shown, this is usually not great. They point out that when very large doses of salicylate are given, a moderate diminution in prothrombin may occur but that this does not result from the small doses used in the ordinary practice of medicine. In fatal cases of salicylate poisoning petechial hemorrhages of the gastro-intestinal mucosa and of the pericardial, pleural and subdural spaces are commonly found. In a fatal case of a 2½ year old child who received at least 150 grains of aspirin, reported by Troll and Menten (1e), hemorrhage was an important symptom, both in the form of a purpuric eruption, and in bleeding from the nose, the bowels and the bladder.

The liver may be affected in salicylate poisoning and a depletion of glycogen has been shown to be present (Lutwak-Mann). Barnett et al (1a) also point out that in their cases the ketosis was greater than could be explained by the starvation or the vomiting, so that an inadequacy of carbohydrate metabolism was probably present. In fact in one case hypoglycemia was demonstrable.

Now that the pathological physiology of salicylism is well understood, the management of salicylate poisoning can be put on a rational basis. Treatment includes giving intravenously, large amounts of fluid, alkali in the form of ½ molar lactate solution, and glucose. Hyperpyrexia, if present, must be reduced by hydrotherapy, but one must not forget that the fever may be due to the infection for which salicylate had been originally prescribed and that this infection needs treatment. When convulsions are present, sedatives are required and if the child is in collapse, oxygen and stimulants must be administered.



## SUMMARY

Three cases of poisoning, one of them fatal, due to acetylsalicylic acid (aspirin) are reported in infants under 1 year of age. The correct dosage of aspirin is approximately 1 grain per year of age every 4-6 hours. The symptomatology of salicylism is discussed and its treatment is outlined. Due to the very extensive use of aspirin in the treatment of infants, salicylism is probably more common than is generally believed. In an infant who presents the picture of fever, hyperpnoea and dehydration without diarrhoea or other evidence of infection, salicylism must be suspected.

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## PIAL MENINGIOMA IN A SIX YEAR OLD BOY

IRA COHEN, M.D.

(New York, N. Y.)

The infrequent occurrence of meningiomas in childhood and adolescence is widely recognized. It has recently been stressed in a comprehensive contribution by Globus, Zucker and Rubinstein (3) in which 92 tumors in that age group were reviewed. Two tumors were classified as pial meningiomas. In their book, "Intracranial Tumors of Infancy and Childhood," Bailey, Buchanan and Bucy (1) detail two cases of true meningiomas in one hundred cases of brain tumors. One of these was associated with multiple neuromas. The incidence of sarcomatous tumors of meningeal origin is larger as it is in the series reported by Globus. Cushing and Eisenhardt (2) in their monograph "Meningiomas" report 295 intracranial meningiomas; only five of these were in adolescents, the youngest being in a child of eight years.

The following case is of interest not only because it presents an unusual type of tumor in childhood, but because of the possibility of multiple tumors.

### CASE REPORT

*Vomiting for 6 months beginning immediately after a tonsillectomy. Attacks of cyanosis for three weeks. Skull plates showed calcification in the posterior fossa. Air studies indicated a right frontal lobe tumor. Tumor removed from right frontal lobe reported pachy-leptomeningioma.*

*History.* A. B. (Adm. #546455), an unusually bright 6 year old boy was referred to the hospital by his pediatrician, Dr. Bernard Denzer in March 1946. Almost immediately after his convalescence from a tonsillectomy in October 1945 he began to vomit. At the onset, this occurred six to eight times a day but diminished in frequency in the course of his illness. Immediately preceding each vomiting the boy complained of a bad taste in his mouth which he stated was like the ether which had been administered for the tonsillectomy. On the basis of this statement the question not unnaturally arose as to the organic basis for the vomiting. The latter was associated with considerable gagging and retching and was not projectile in character.

Beginning about three weeks prior to his admission to the hospital he developed spells in which it appeared as though he would choke. His face turned blue and he would hang on to objects for support lest he fall. These attacks would last about one half minute and were frequently followed by a slurred type of speech. There was no complaint of headache.

In his past history the only severe illness was a week's illness associated with fever to 103 degrees, diagnosed as "intestinal grippe."

*Examination.* The boy was most cooperative. He was left handed. His mentality was well beyond his years. Many pigmented spots were noted over the body. Percussion of the head elicited a MacEwen's sign. The deep reflexes were all equally depressed. Plantar response was not as good on the left as on the right. There was no motor or sensory defect. The sense of smell was normal. The fundi showed disc margins which were not quite sharp. There was a posterior polar opacity of the right lens. The examination of the function of the other cranial nerves including taste failed to show any abnormality.

*Laboratory Data.* The blood picture was normal as was the urine analysis. Lumbar puncture yielded clear fluid at an initial pressure of 140 mm. water. It contained no cells. A gastrointestinal x-ray series was normal. The electroencephalogram showed no ab-

normality. The skull plates showed a group of punctate calcifications in the cerebellum and some widening of the fronto-parietal suture (fig. 1).

*Course.* During the first few days of hospital residence he was observed in several



FIG. 1. Calcification shown in posterior fossa



FIG. 2. Pneumoencephalogram showing deformity of right lateral ventricle and the calcification in the posterior fossa

attacks. There was an aura of a taste of ether and a peculiar feeling in the epigastrium. The "attack" was essentially a stiffening of the body, associated with cyanosis and drooling of saliva. Vomiting took place almost daily, sometimes several times a day. It was not projectile.

At this time the diagnosis was entertained of a brain tumor localized in the posterior fossa on the basis of the x-ray films of the skull. This localization did not, however, take

into account the suggestive history of uncinate phenomena associated with the choking attacks. In view of the multiple skin nevi the possibility of multiple hemangiomas was considered since this type of tumor is one of the more common ones in children and may be multiple.

A ventriculogram was unsatisfactory. An encephalogram showed only a possible slight shift of the ventricular system to the left. The right anterior horn was compressed anteriorly and displaced upward (fig. 2).

On April 3, 1946 under ether anesthesia a flap was turned down exposing the right fronto-temporal region. The Sylvian vessels were enlarged but not displaced. At a depth of 4 cm. from the surface a resistance was encountered in the pre-motor area. A well encapsulated tumor was removed from the depths of the fronto-temporal lobes. Measured in the laboratory the largest of three portions measured 6 x 4 x 3 cm. The histological diagnosis was reported by Dr. Globus as pachy-leptomeningioma.

A left hemiplegia followed the operation. This was complete in the immediate post-operative stage but showed signs of beginning improvement at the time of the patient's discharge from the hospital on the 15th post-operative day. In spite of the fact that he was left handed there was no speech defect at any time. Four months after operation he was walking and moving the upper arm. There was practically no motion in the fingers.

*Comment.* The onset of the symptoms immediately following a tonsillectomy, and the predominant symptoms being gagging, vomiting and the taste of ether led to the consideration of a psychic rather than organic basis for the clinical picture. The precocious mental development of the boy, the decrease in frequency of the vomiting coupled with the absence of localizing signs gave additional weight to this consideration.

The tumor was so situated that it could have been responsible for the uncinate symptoms without giving any other localizing signs. The calcification in the region of the cerebellum shown in the x-ray films has the appearance of calcification in a tumor. Verification of this will have to await future developments.

#### SUMMARY

A case history of a meningioma in a six year old boy is reported.

The onset and early course suggested a psychogenic basis for the symptoms.

Calcification in the posterior fossa was noted in the x-ray films which may indicate a tumor in addition to the right fronto-temporal meningioma removed at operation.

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## THE CLINICAL SIGNIFICANCE OF BILIARY, PANCREATIC AND DUODENAL REFLUX

RALPH COLP, M.D.

(New York, N. Y.)

*From The Surgical Services of The Mount Sinai Hospital, New York, N. Y.*

The anatomical variations of the periampullary region of the duodenum, and the dysfunctions of the sphincter of Oddi, may occasionally play important roles in the physiological activities and pathological processes of the biliary tract and pancreas. They undoubtedly are responsible for certain types of acute pancreatitis and acute cholecystitis, some forms of jaundice, and many of the unfavorable results following a cholecystectomy.

Oddi (1), in 1887, while trying to explain the presence of a dilated biliary tract in cases in which the function of the gallbladder had been lost, accurately described the common bile duct sphincter. But it was not until 1901, when Opie (2) reported a case of acute hemorrhagic pancreatitis due to the presence of bile in the pancreatic duct, that the importance of the anatomical relationships of pancreatic and bile ducts to the ampulla of Vater were recognized and appreciated.

Opie's classical case report stimulated anatomical, roentgenological and experimental interest in the periampullary region of the duodenum in order to determine the frequency of those anatomical variations which made possible the retrojection of bile into the pancreatic duct. Mann and Giordano (3) reported that this possibility was present in 3.5 per cent of their dissections of cadavers. Schmieden and Sebening (4), from roentgenologic lipiodol studies of the injected ducts, concluded that this anatomic arrangement was present in 20 per cent of their cases. Subsequently, Cameron and Noble (5), by occluding the papilla with a small stone and pouring Woods metal into the choledochus, noted that the pancreatic duct was present in the mold of 75 per cent of their preparations.

However, there are other factors aside from a biliary calculus which may obstruct the ampulla. It may be either occluded reflexly, or closed directly by the edema and spasm incident to the passage of a calculus, or by an inflammatory or neoplastic enlargement of the pancreas.

Undoubtedly edema of the papilla and spasm of the sphincter of Oddi not infrequently cause ampullary occlusion. Balo and Ballon (6) reported the necropsy findings in four cases of simple catarrhal jaundice without stone in which the swelling and edema of the duodenal papilla probably caused a simultaneous retention of both pancreatic juice and bile.

The importance of spasm of the sphincter of Oddi has been stressed and verified by the experimental work of Archibald (7). This was further corroborated by Westphal (8) who made a detailed physiological study of the muscles



near the choledochal and pancreatic orifices, and emphasized their functional importance in normal and pathological processes. He further demonstrated that in forty-two of fifty cadavers, the anatomical relationships in this area were such as to make possible either the reflux of bile into the pancreatic duct, or the reflux of pancreatic juice into the choledochus.

The factor which determines the direction of flow is probably the relative secretory pressures of the biliary and pancreatic fluids. The pressure as a rule is higher in the pancreatic duct, which accounts for the greater frequency of a pancreatic, rather than a biliary reflux. However, in some instances, if the accessory duct of Santorini is present and communicates with the duct of Wirsung, the resultant diminution of pressure in the main pancreatic duct may permit the bile to flow into the pancreas.

While the presence either of bile in the pancreatic duct, or of pancreatic juice in the choledochus may be perfectly innocuous, it may stimulate various degrees of acute inflammatory reactions under certain circumstances. A biliary reflux may cause either an edema of the pancreas or an acute pancreatitis, and a pancreatic reflux may result in either a non-perforative biliary peritonitis, an acute cholecystitis, a chronic choledochitis, or rarely a stricture of the common bile duct.

#### BILIARY REFLUX

Biliary reflux is not solely responsible for the pathogenesis of acute pancreatitis. Pancreatic inflammation may also be caused by infection entering either the ducts of Wirsung or Santorini directly from the duodenum, or the main pancreatic canal via the choledochus. Acute pancreatitis may result from embolism or thrombosis, from contact with suppuration in the adjacent viscera, and from either direct or indirect trauma. The etiology was varied in our series of acute pancreatitis (9). In eight autopsies in which the finer anatomy of the periampullary region was described, biliary reflux was possible in six. But in these cases it could not be definitely stated that bile was the cause of the pancreatitis because the edema, hemorrhage and necrosis present at the time of autopsy may have obscured its presence.

The pathologic mechanisms by which retrojected bile causes pancreatitis has been fully discussed by Dragstedt et aliter (10). It is likely that the pancreatic parenchyma is destroyed by the local cytolytic and destructive properties of the bile salts, and not by the activation of the intraductal trypsinogen of the pancreatic juice. The toxic effect of the bile salts is neutralized by the proteins of the blood serum, so that the hemorrhage and exudation are protective phenomena. The digestion of the protective serum by the proleolytic enzymes of the pancreatic juice frees the bile salts for further destructive action.

The following case graphically illustrates the role of bile as a cause of a mild acute pancreatitis.

*Case 1.* (Adm. #380515.) A female, 51 years of age, was admitted to The Mount Sinai Hospital on June 2, 1935 and discharged on July 14, 1935. A cholecystectomy was performed eight years previously with a subsequent history of fatty food intolerance. Three

months prior to admission, the patient experienced three attacks of epigastric pain with vomiting, severe enough to require morphine.

Physical examination disclosed a well nourished female with a well healed upper right scar. The blood pressure was 124 systolic, 85 diastolic. The urine was negative. The icteric index was 6. While in the hospital the patient suffered another episode of epigastric pain and became jaundiced, the icteric index rising to 45, and the blood amylase to 42 units.

Exploration under spinal anesthesia was performed. The cystic duct stump was so enlarged as to resemble a rudimentary gallbladder. The common bile duct was dilated to 1 inch in diameter. The pancreas felt hard, almost carcinomatous. The common bile duct was opened and two facettted stones were removed. A probe passed readily into the duodenum. A piece of pancreatic and of liver tissue were removed by means of the Hoffman punch. A T tube was inserted into the choledochus. The patient made an uneventful postoperative recovery and the T tube was removed on the fifteenth day.

Pathological examination of the pancreas showed acute interstitial pancreatitis with biliary deposits in the pancreatic ducts.

These sections are proof of the entrance of bile into the pancreatic ducts. In addition, the increase of diastase as well as bilirubin in the blood speaks for obstruction of both ducts. Undoubtedly one of the facettted choledochal stones temporarily blocked the ampulla, making possible the biliary reflux.

Biopsies of pancreatic tissue are seldom taken because of the fear of causing an acute pancreatitis. If this procedure were done more regularly, it is probable that the bile would be found to be responsible for many cases of pancreatic edema and acute pancreatitis.

#### PANCREATIC REFLUX

This is probably more frequent than biliary reflux. The occasional occurrence of severe skin digestion about a choledochostomy should suggest the presence of pancreatic juice in a biliary fistula, which can be verified readily by chemical examination for the ferments.

Nordmann (11) recorded two cases of acute pancreatitis in which pancreatic ferments were present in the drainage from a choledochostomy, and Westphal (12) also demonstrated large quantities of ferments in a dilated choledochus. In a series of twenty-four cases of common duct stones in which a choledochostomy was performed (13), evidence of pancreatic ferments were found in eight instances. In six of these patients the pancreatic duct was visualized by lipiodal injections (14). It seemed logical to assume that the ferments were derived refluxly from the pancreas rather than from the duodenum inasmuch as insoluble carmine crystals given orally did not appear in the operative wound.

In a case recently observed, the periodic spasm of the sphincter was definitely demonstrated by lipiodol studies and recorded by kymographic tracings, and its role in the causation of a pancreatic reflux was further evidenced by the occasional presence of amylase in the biliary drainage.

*Case 2.* (Adm. #382140.) C. F., a 60 year old housewife, had suffered from attacks of gallbladder pain for five years. With the last attack, twelve days before operation, jaundice was noted. The icteric index was 50 and the bilirubinemia 2.0 mgm. per cent. At operation, the gallbladder was found full of stones and acutely inflamed. The common duct was thickened, enlarged to twice its normal diameter, and filled with a sand-like precipitate,

but contained no stones. Cholecystectomy and choledochostomy were performed. Urobilin was not present in the stools until the nineteenth day. Pancreatic enzymes were demonstrated in the biliary drainage on several occasions. On the third day, the initial resistance of the sphincter was 225 mm. H<sub>2</sub>O, and those following were constant at 185 mm. H<sub>2</sub>O. On the sixth day after operation, the constant resistance was even higher, remaining at 225 mm. H<sub>2</sub>O. On the tenth day the injection of lipiodol outlined the hepatic ducts extensively, and only a few droplets of lipiodol entered the duodenum. The following day no lipiodol was evident in the duodenum, but some still remained in the choledochus, while the remainder was seen in the dressings.

Pancreatic ferments however are not as infrequently present in the bile as these few isolated instances would seem to indicate. In a recent communication, Popper (15) stated that the bile (usually from the gallbladder) was examined in two hundred and nineteen surgical patients for the purpose of finding pancreatic ferments. The samples were obtained from cases of cholelithiasis, tumors of the pancreas, acute pancreatic disease, and from those with a presumably healthy biliary system. Diastase was demonstrable in 17 per cent of the cases. The cases in which the bile ducts contained pancreatic juice differed in no way from other cases of cholelithiasis in respect to history, symptomatology, clinical course, operative findings, or postoperative course. Subsequent follow-up examinations made months or years later failed to reveal indications either of pancreatic or hepatic dysfunction.

While pancreatic ferments in the bile may be of little moment in the majority of cases, they may be of great pathologic significance in others. They may cause, under certain circumstances, either a non-perforative bile peritonitis, or an acute cholecystitis. In 1910, Clairmont and Haberer (16) reported a case of bile peritonitis without demonstrable perforation of the bile passages. They suggested that this might have been caused by an alteration in the permeability of the bile duct walls. Blad (17) subsequently offered an explanation for these unusual cases on a basis of his chemical and animal experiments. He felt that the pancreatic ferments aided by bacterial action digested the colloids of the bile, and liberated the bile pigment which by some unknown process could then pass through a membrane. Westphal (12), by the injection of human pancreatic juice into the choledochus of animals, was able to produce acute and chronic pathologic changes in the liver, gallbladder and extrahepatic bile ducts, many of which were comparable to those found in the human. He felt that this particular action of trypsin, while uncommon, was an important factor in the production of cholecystitis, together with infection, lithiasis, stenosis and motor dysfunction of the biliary passages.

Wolfer (18) subsequently verified Blad's observations and some of Westphal's by a series of ingenious experiments based upon the entrance of pancreatic juice into the gallbladder. He concluded that these ferments devitalized the gallbladder wall so markedly that a bacterial invasion, especially anaerobic, was favored. The violent reaction of the gallbladder mucosa might also be caused by a change in the ordinarily acid medium of the gallbladder bile to an alkaline one, by the presence of pancreatic juice.

Dragstedt, Haymond and Ellis (10) have recently summarized other factors

which might partially explain the production of acute cholecystitis by pancreatic reflux. Non-activated pancreatic juice as it exists in the duct system of the pancreas is non-toxic, either on intravenous or intraperitoneal injection, and even activated trypsin does not destroy healthy living tissue. Bile apparently produces its local toxic and cytolytic effects through the bile salts which have been shown to constitute the toxic elements in bile. Gallbladder bile, because of its greater concentration of bile salts, should be, and undoubtedly is, more effective in its destructive activity than hepatic duct bile. The acid reaction of the bile in the gallbladder tends to neutralize the destructive effect of this increased concentration of bile salts. Bile as it is secreted by the liver is invariably alkaline, whereas under normal conditions the bile in the gallbladder tends to be kept acid through the selective concentrating activity of that organ. Bile salts are far more soluble, and, therefore, much more toxic under alkaline than under acid conditions. If a large quantity of pancreatic juice enters the gallbladder, the alkalization of the normally acid gallbladder bile, plus the presence of pancreatic ferments probably activated by infected bile, produce conditions favorable for tissue destruction. In addition, the activated trypsin may act in several ways. It may digest the proteins which have a definite protective action against the destructive effects of the bile salts. It may remove the taurine and glycine from the conjugated bile salts, liberating the more toxic free bile acids. Finally, trypsin may be considered as an active catalyst, accelerating a reaction which otherwise would take place slowly, thereby increasing and enhancing the toxic effect of the bile.

Clinically active pancreatic ferments in considerable quantities have been found in the bile of acutely inflamed gallbladders, and their presence appears definitely related to the acute inflammatory process present. Such instances have been reported by Bundschuh (19), Ruppanner (20), Dziembowsky (21), and Brackertz (22). Three similar cases of acute cholecystitis associated with the presence of appreciable quantities of pancreatic enzymes in the gallbladder bile have been observed on the services of the The Mount Sinai Hospital (23). In two of these cases, operative intervention disclosed free bile in the peritoneal cavity, and in one, fat necroses were seen not only in the acutely inflamed gallbladder wall, but also in the adherent omentum. The gallbladder bile which was aspirated at the time of operation, was definitely alkaline, and diastase was present in large amounts in all three cases. The cultures were sterile in two cases, but in the third, *bacillus coli* and *bacillus Friedlander* were present. No bacteria were found in the microscopic sections of the gallbladder in any of the three cases.

The amount of the ferments present could only have been accounted for by a pancreatic reflux. The reflux of duodenal juice charged with pancreatic ferments into the bile ducts can readily be excluded together with the assumption that the enzymes were excreted by the gallbladder mucosa into the bile, or entered it through the blood or lymph streams.

Pancreatic reflux as an initiating or precipitating cause of acute cholecystitis is probably more common than the paucity of the reported cases would seem to

indicate. If pancreatic ferments are found as frequently as Popper reports, cognizance must be taken also of the role in the possible production of chronic gallbladder disease as originally suggested by Westphal.

Whipple reported three cases of irreparable stricture of the choledochus in which he felt sure that the common bile duct had not been injured at the time of the primary cholecystectomy. When these patients had become deeply jaundiced, requiring a second exploration, the common duct seemed to have been entirely replaced by a shred of dense connective tissue extending from the portal fissure to the duodenum. He felt that such an extensive destruction of the common bile duct could only be explained by an activated pancreatic reflux. It is barely possible that those cases of chronic choledochitis, described by the French surgeons, in which the common duct resembles a pipe stem, and into which a fine probe could not be introduced, may have been due to a repeated pancreatic reflux rather than to the effects of biliary stagnation.

#### DUODENAL REFLUX

The reflux of duodenal contents through the common bile duct is exceedingly rare. The outline of a common duct by air or following barium x-ray examination of the gastrointestinal tract is a most unusual finding. McArthur (24) reported a case in which a choledochal stone was coated with barium evidently derived from the duodenum, and Jennsen noted a case in which the common bile duct was outlined with barium. Postoperatively, too, duodenal reflux is most unusual. Codman (25), Davis (26), have reported cases of this character. Two cases have been observed on our wards. The diagnosis of the condition presents very little difficulty. Walters (27) states that following a choledochostomy, the drainage of a large amount of fluid material within the twenty-four hours, or the digestion of the skin about the drainage tube, should make one suspicious of a duodenal reflux, and if methylene blue is given by mouth, it should appear about the abdominal sinus or stain the drainage. In our experience insoluble carmine crystals given by mouth are more easily recognized than methylene blue in the drainage from a duodenal reflux.

The infrequency of this complication following the removal of an impacted calculus from a dilated ampulla, and in those cases in which the sphincter of Oddi is willfully divided, or forcibly stretched with graduated sounds, demonstrates the point emphasized by Coffey (28) in his experimental work on the transplantation of the common bile duct into the duodenum, and the ureter in the colon. The orifice of the common bile duct is not solely protected by the sphincter of Oddi. Its oblique entrance through the wall of the hollow duodenum produces the effect of a one way valve, effectively preventing the entrance of intestinal contents into the common bile duct. Evidently the paralysis of the sphincter alone does not predispose to duodenal regurgitation.

On the other hand, if the entire periampullary region of the duodenum is side-tracked by a choledochoduodenostomy which is occasionally indicated in cases of stricture, stones, or malignancies involving this particular area, duodenal regurgitation into the extrahepatic ducts is not infrequent, but evidences of ascending infection are not common.



In 1923, Hoserman (29) reported a case in which fourteen months after a choledochoduodenostomy for a carcinoma of the head of the pancreas, there was x-ray evidence of a regurgitation of barium in the choledochus, the hepatic duct and their branches. The patient died a month later. Autopsy disclosed a carcinoma of the pancreas with metastases to the liver and lymph nodes, a patent biliary duodenal anastomosis and obliteration of the cystic duct with atrophy of the gallbladder. There was no evidence of cholangitis. Sasse (30) reported ten cases of choledochoduodenostomy, Floerken (31), fifty-four cases, and Peterman (32) twenty-two cases, without any evidence of postoperative cholangitis. All of these surgeons, however, freely granted that this was a possibility.

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## MARRIAGE AND MATERNITY, AS AFFECTED BY DIARRHEAL DISEASES

BURRILL B. CROHN, M.D.

(*New York, N. Y.*)

The physician, specialist or practitioner, upon whom devolves the doleful duty of treating chronic diarrheal diseases, is often confronted by the personal problems of his patients, problems which pose intricate questions of procedure as to sex, romance, marriage, child-bearing. Shall a patient, male or female, who is a sufferer from ulcerative colitis, a disease of always doubtful cure and constantly subject to a recurrence, be allowed to marry, accept domestic responsibilities, bear children, and assume the onus of rearing a family?

Ulcerative colitis is a disease of long chronicity; one rarely uses the word "cured" with any sense of confidence. The disease has a great tendency to recur even with the best economic and psychological circumstances. The percentage of permanent cure, that is cessation of all symptoms over a course of years, is small. Since women, and particularly young women, are equal sufferers with men, the question of marriage and child-bearing is often a decision of great moment. Such questions are often put to the physician, whose answer should decide such issues as: is marriage detrimental, will pregnancy aggravate the disease, will childbirth cause a recurrence of the diarrhea? When the patient is one of those unfortunates who is condemned permanently to wear an ileostomy bag, the decision as to marriage and pregnancy becomes all the more complicated.

For example, the relationship between chronic, or acute, ulcerative colitis and menstruation is a significant one. During the acute phase of the disease or during an acute recrudescence of a chronic form, the menses cease when the infection is severe and the diarrhea is unchecked. What the relationship is, and what the mechanism may be, is little understood, but the fact remains that during the serious phase of the illness amenorrhea is a common manifestation. The first return of even a scant menstruation is a prognostic sign of significance and usually ushers in a remission of all the symptoms.

As to pregnancy, it is a consensus that during gestation cases of colitis do well. During the acute or the serious chronic but active stage of diarrhea, pregnancy is obviously unwise and is rarely undertaken by marriage partners. But when a safe remission has been achieved, and weight, strength, and blood volume have been restored, the young wife will claim her rights to maternity. A woman who becomes pregnant during the remission or healed stage of colitis will probably do very well during the period of gestation.

This well-being during pregnancy is also common with patients who are sufferers from chronic peptic ulcer of the stomach or the duodenum. Sandweiss and his collaborators (1), in an important article on "The Relation of the Sex Hormones to Peptic Ulcer" have summarized the present knowledge on the

subject and have added some interesting clinical and experimental data of their own. In over seventy thousand cases of pregnancy admitted to five Detroit hospitals, only one case of active ulcer was noted. If chronic ulcer had been present before pregnancy, the symptoms disappeared and normal gestation and parturition was the rule, with very few exceptions. Experimentally, the injection of anterior pituitary hormone (antuitrin S) prevented the formation of ulcers in the Mann-Williamson dogs (98 per cent mortality in the untreated dogs); in an additional twenty per cent of the dogs the ulcers were shown to be in the healing stage at the time of sacrifice.

The colitis case, like the ulcer patient, takes her pregnancy well, but recurrence after parturition is so common as practically to constitute a large majority. The flare-up of the diarrhea and fever may occur within a few days or more likely within a few weeks of the delivery, and may be extremely severe.

An interesting experience in clinical bedside diagnosis will well illustrate this point. A young wife, delivered twelve days previously of a healthy child, developed severe diarrhea and fever during the puerperium. There had been no definite previous history of diarrhea; neither x-ray studies nor sigmoidoscopy was possible because of the severity of the symptoms and the grave prostration. Previous consultants had made the diagnosis of acute regional ileitis, because of abdominal tenderness, fever, pain and diarrhea. Without laboratory data or proctoscopic examination a differential diagnosis between ileitis and colitis was not scientifically possible, but one fact seemed to weigh the balance. Ileitis is generally not affected by pregnancy nor does parturition lead to a recurrence. But recurrence of colitis promptly after parturition is almost the rule. In fact, in an isolated instance the recurrence of the disease occurred in the fifth month of gestation though this is an exceptional incident. Therefore, the diagnosis of ileitis in this case was questioned and was replaced by one of acute ulcerative colitis, a reversal of opinion which was later verified by x-ray and sigmoidoscopic examinations.

The primary question, therefore, arises as to the advisability of marriage for the chronic female sufferer from colitis even when a prolonged period of remission gives a fair assurance of health. It is obviously detrimental to the psychology and the morale of a young woman to permanently deny her romance, sex and marriage. The bearing of children is an integral part of the marriage bond. Colitis is definitely one of psychosomatic diseases, subject delicately to psychic upsets and frustrations, likely to undergo violent recurrences of the diarrheal phase when exposed to emotional trauma. Under such circumstances we cannot long hold out consent to marriage, even though the admonition against pregnancy was concurred in by both parties to the marriage.

A young woman in a remission stage of severe ulcerative colitis requested advice and permission as to marriage from her physician. The condition was agreed upon that the prospective husband be fully apprised of the possibility of a recurrence of the disease in his spouse, and also of the need for the denial of pregnancy. In the presence of both prospective parties to the marriage all debatable conditions were fully exposed and laid on the boards. "No punches

were pulled" as one would say in the vernacular. After full admonition as to the facts the couple decided to marry with the understanding that child-bearing was prohibited. Within a few weeks of the marriage a severe recurrence of diarrhea, fever and prostration occurred in the wife, even though sexual relations had not been consummated. After the passage of a few months of severe illness, the husband became estranged and soon sued for divorce on the grounds that fraud had been perpetrated and that he had been falsely allowed to marry an "invalid." The psychosomatic strain of the romance and of the marriage was too great, and the recurrence of the disease was the sequel much to the unhappiness of those concerned and much to the chagrin of the advising physician.

It is impossible to deny an apparently well woman marriage for an indefinite period. She will eventually marry even though it be against the advice of her practitioner and may even insist upon her right to bear children. Many of these marriages are very successful and in some of them one or more children have been born without recurrence of the malady. Nevertheless the physician must continue to advise and to explain the possible dangers and by so doing he will reduce the responsibility for any mishaps that may occur.

Ileostomy as a permanent procedure is often practiced as a life-saving measure in protracted ulcerative colitis. It is frequently performed in a young person since colitis is essentially a disease that affects persons in their early decades of life. The problems of a romantic or sexual nature that arise when a young person is forced to wear a permanent ileostomy bag are very intricate. The sex life of a man with an ileostomy is abridged but is not impossible. He may work, play, love, indulge in sexual intercourse and may take his part as a full fledged member of the community. Many young men with ileostomies have married and been the father of healthy children. The romantic love of a woman for a man is often so overwhelming, the maternalistic attitude of a woman toward an "invalid" so natural, that even the handicap of the ileostomy will be forgotten.

Not so, however, with the woman patient and the fastidious attitude of a male consort toward his proposed sex-mate. Marriage of a man to a girl with a permanent ileostomy is unlikely and rarely holds permanently. Usually an ileostomy performed upon a girl bars romance, bars sex and inhibits all thoughts of marriage and child-bearing. For that very reason it is mandatory to reflect, before requesting the performance of an ileostomy, upon the long course effect of the procedure as it influences her future personal life. One may save a life but at the cost of eliminating sex and marriage without which any normal female will feel a sense of complete frustration. Many a young woman has under these circumstances expressed herself as being quite ungrateful that her life has been protracted; she may not thank her physician for the added years of incomplete life granted to her.

When serious colitis occurs in a woman who has been married for some years, the necessity of performing an ileostomy as a life-saving procedure introduces a very similar problem. An ileostomy is repugnant to sex; the marriage partner,



the husband, may become discouraged and seek his love and his sex outlet outside of his marriage. The danger of resultant infidelity on the part of the husband is not theoretical but is real. Even though infidelity does not occur, the constant threat and the perpetual fear that it may have taken place is likely to lead to a fixed anxiety state and a fear neurosis in the wife.

It is fortunate that regional ileitis presents few of these complicated problems of a personal or a romantic nature. For ileitis is a curable disease, and when well operated should fully restore life and function. A woman who has been successfully operated and who has subsequently been healthy for a sufficient period of years to make late recurrence of the disease most unlikely, may marry and bear children without danger to her health or to the pregnancy. Pregnancy and parturition do not cause a recurrence of the disease, nor does the operative procedure, resection or short-circuiting, seem to affect adversely a normal delivery. In contrast to ulcerative colitis, ileitis is a low-grade and mild disease; menstruation is rarely affected even during exacerbations, pregnancy is not affected. The undesirability of carrying through to term during the active phase of the disease, however, makes a therapeutic abortion often a mandatory procedure. But the healed and successfully operated case may carry on as a normal individual; no inhibitions as regards sex or marriage or childbirth need be observed.

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## ECTOPIC PREGNANCY

A STUDY OF 174 CASES

W. C. DANFORTH, M.D.

(*Evanston, Illinois*)

In a previous communication R. M. Grier reported a series of 100 cases of ectopic pregnancy from our service. The mortality in this series was 3 per cent. Since the publication of this paper 74 more cases of ectopic pregnancy have accumulated. With the desire of ascertaining what our more recent results have been this later group has been studied.

The diagnosis of unruptured tubal pregnancy is difficult. For this reason in almost all published groups of cases, the great majority of patients, whose cases are studied, are not seen until after rupture has taken place. The safety of the patient depends to a great degree upon the amount of time which elapses between the onset of intra-abdominal bleeding and the institution of surgical management. While recognition of the presence of a tubal pregnancy after rupture is easy in many cases, there is a considerable group in which diagnosis is difficult. In these a loss of time with consequent increase in the amount of blood loss, is likely to occur.

The most common single symptom is pain. It was present in every case of the series reported by Grier, while in 70 of the last 74, pain was felt. It varied in severity but was usually in the lower abdomen, on one side or the other. The pain is not invariably complained of on the same side as that upon which the pregnant tube is found. It may be quite severe and cramp-like in character while in other cases the pain may be of less severity. A violent pain is not essential for diagnosis. In some cases it may be referred, as for example, in the case of a patient who complained of pain in the epigastrium. In one of our recent cases, in which an abdominal pregnancy of about four months was found, the patient had complained of rectal distress. The large mass was found to fill the cul-de-sac.

Pain in one or the other or both shoulders occurs with a fair degree of frequency. In this entire series it was found in 27 cases. This is produced by the migration upward of blood along the colonic gutter until it comes to lie above the liver, between its convex surface and the diaphragm. It usually is found in women who have suffered syncope following the loss of blood so that the body has, at least for a time, occupied the horizontal position. The significance of this symptom, in women in whom ectopic pregnancy is suspected, has been emphasized by Rubin and by myself. In a woman in the reproductive years, in whom regular bleeding has occurred, with abdominal pain, the signs of blood loss and perhaps amenorrhea, it speaks very strongly for the presence of ectopic pregnancy, especially if no abdominal trauma has occurred. Amenorrhea is not invariably present. In the first 100 cases there were 24 in whom no period was missed. In summarizing the last group this symptom was omitted.

One of the most significant symptoms is bleeding. In the first 100 it was noted in 88 per cent of the cases. In the second series of 74, bleeding occurred in 44 cases, or 59 per cent. In many cases it had gone on for some time, in a few cases from two to four weeks. It usually was not severe and the histories of some patients refer to it as spotting. The patient sometimes confuses it with a period. Irregular bleeding, especially if it follows a failure to menstruate at a normal time, if accompanied by or followed by abdominal pain, demands the consideration of ectopic pregnancy as a possible cause of the symptoms. Sometimes bits of decidua may be expelled. Should this occur one should seriously consider the presence of ectopic pregnancy. This statement should be considered in relation to what will be said in a moment concerning curettage as a means of diagnosis.

Lower abdominal tenderness is almost constant. The presence of free blood apparently plays a part in the causation of pain although the distension of the tube is also an important factor. The irritating effect of the free blood is evidenced by the very frequent presence of leukocytosis. In 138 of the entire group the white cells numbered 10,000 or more. In the last group of 74 there were 4 cases in which the count ranged from 10,000 to 20,000. In 5 cases the count ranged from 20,000 to 30,000. There were 6 cases in which it was over 30,000, the highest being 37,000. In 12 cases the leukocyte count was less than 10,000; in the remainder it was not recorded.

The leukocyte count is a transitory one. If a small hemorrhage occurs the count may rise and then, within 24 hours, decline to rise again when further bleeding takes place. When a very early ectopic pregnancy is suspected, and differentiation between it and other lower abdominal conditions must be made, this point is sometimes of value.

While the white count is frequently of value in diagnosis, the red count must be used guardedly. A count made soon after severe intra-abdominal hemorrhage will often give results which are nearly or quite normal. The blood which has escaped into the abdominal cavity, although the amount may be large, reduces all elements of the circulating fluid equally. Plasma as well as cells escape and that which remains may retain the normal balance between plasma and cells. A count taken twenty-four hours later, after the introduction of fluid, may give a decidedly different result. If the count is made after more than one intra-abdominal loss of blood has occurred, the initial count may show anemia.

Cullen in 1919 drew attention to a sign, which is known by his name. The appearance of a bluish discoloration about the umbilicus indicates the presence of blood in the peritoneum. If this sign is seen in a woman who is in her reproductive years, who has abdominal pain, irregular bleeding and perhaps amenorrhea, the presumption of ectopic pregnancy with hemorrhage is very strong. In this series it has been seen only once so that its usefulness cannot be great inasmuch as it appears only in a very small minority of cases.

Vaginal findings may vary from the presence of a large mass to completely negative findings. In one of our cases nothing could be felt by bimanual examination although ectopic pregnancy was suspected. A transitory leukocytosis

of moderate degree was present. This disappeared over night to reappear the following day with a recurrence of pain which was not severe. On the second day some tenderness was elicited on the affected side but still nothing could be felt. A very small and presumably quite early tubal pregnancy was found. With a history suggestive of ectopic pregnancy the finding of a very tender mass on either side or in the cul de sac, or the presence of a boggy mass in the cul-de-sac which may be clotted blood, is strong evidence. The pregnant tube may, in some cases, be found in front of the uterine body.

Curettage with examination of the curettings for decidual cells has been often recommended. This was not discussed in the original report but in the last series of 74, curettage was done eight times. Decidua was found twice. If curettage is to be utilized as a means of diagnosis it should be with a full realization of its limitations. If the patient has been bleeding for some days the decidua may have been cast off. It is of much more value in patients whose bleeding is recent. The failure to find decidua does not rule out the presence of an ectopic pregnancy although its presence, with a complete absence of villi, speaks for it. If curettage is done, the relationship of the time at which it is done with the length of the bleeding should always be considered. My own estimate of its value is such that I have never made use of it in the cases which I have personally managed. In one case a laparotomy was performed four days after a curettage which produced scrapings in which decidua was found. If the symptoms were sufficiently definite to suggest the performance of curettage a more rapid means of settling the doubt, either by colpotomy or a short abdominal incision, would have saved the patient the risk of bleeding during the waiting period.

During the earlier part of the time when the first group of cases was gathered, the Aschheim-Zondek test or its modifications such as the Friedmann test, were not available. In the last group of 74 a positive Friedmann test was obtained twice. The value of the pregnancy test, which requires forty-eight hours for completion, cannot be great for it can only be utilized in those cases in which an unruptured pregnancy is suspected and which are far enough advanced in pregnancy that one may, with confidence, expect a positive test to be had. In the great majority of these patients, who enter the hospital after rupture, time does not permit the use of a diagnostic method which requires this amount of time.

I believe that no series of ectopic pregnancies of any size has been reported with the correct diagnosis in all cases. In the earlier series an incorrect diagnosis was made in 14 per cent of the cases. In the late group a diagnosis of twisted ovarian cyst was made three times, four patients were supposed to have had appendicitis and in one case a diagnosis of incarcerated gravid uterus was made. In this last one the real condition was abdominal pregnancy. In the last series of 74 an incorrect diagnosis was made in 10.8 per cent.

The character of the tubal pregnancy was not noted in the first series but in the last 74 there were 30 which were in the distal third of the tube and eight in the mid portion or the isthmus of the tube. It is unfortunate that more accurate

descriptions of the pelvic findings did not appear in more of the operative notes. Abdominal pregnancy was found twice in the last 74 and not at all in the first 100. In the last series one case of ovarian pregnancy was found. This has been reported elsewhere.

The majority of women who suffer from ectopic pregnancy do not die from the first hemorrhage. There is usually time enough, after the first loss of blood, which is practically always accompanied by pain, to arrange for the necessary surgical management. It is important, therefore, that the condition be recognized early in as many cases as possible. This, unfortunately, does not always happen. In one case, seen in consultation in another hospital, under the care of a physician who enjoyed the title of obstetrician to the institution, the patient had been in the hospital for two days and had had one attack of pain before admission. Another had occurred after admission. A very typical history had not aroused suspicion and a massive accumulation of blood was found in the abdomen. Another patient, whose history is among those of the first group of 100, had been observed all day by her physician who had even carried out transfusion. The gynecological consultant who was ultimately called recognized the condition but immediate surgical care was too late to save the woman's life. As is indicated by the proportion of correct diagnoses given here it is possible, in most cases, to recognize the presence of an ectopic pregnancy, especially after rupture of the tube. Even in those in which an exact diagnosis is not possible, the presence of an intra-abdominal condition requiring immediate attention should be evident.

In the great majority of cases immediate surgical attack is the best treatment. In the entire series there were four patients who entered the hospital in shock. If the condition of the patient is extremely bad, one may delay long enough for a measure of recovery to take place, or for transfusion or plasma to be given, but the control of bleeding at the earliest moment remains the keynote of management. Only one patient in this series was treated without operation. This patient recovered. Her history and physical findings were so characteristic of ectopic pregnancy that she is included here. A private patient of my own, who ultimately lost both tubes because of repeated ectopic pregnancies, undoubtedly had two attacks of tubal pregnancy with expulsion of the tubal contents through the fimbriated end without operation. These two conservatively treated attacks are not included here.

It is suggested that the term tubal abortion be abandoned. It is an improper expression as no abortion takes place. The tube ruptures, either into the free peritoneal cavity, into the space between the layers of the broad ligament or into its own lumen. Intra-tubal rupture is a common occurrence in the rather frequent ampullar type of ectopic pregnancy. The tubal lumen fills with blood by which it may be greatly distended. Blood clots, or products of conception, or both protrude through the fimbriated end of the tube. This escape of blood together with a part or all of the tubal conceptus has been termed a tubal abortion. This designation should be given up. It is far more accurately descriptive of what is taking place to refer to it as an intra-tubal rupture.



All of the cases in this series were dealt with by means of laparotomy with the exception of one. In this case the pregnant tube was removed vaginally. Colpotomy for diagnosis was done eight times in the entire group. In each case free blood was found and in all but one the colpotomy wound was closed and the abdomen opened.

Colpotomy will quite definitely indicate the presence of blood in the *cul-de-sac*. If one wishes to make a vaginal exploration for the purpose of ascertaining whether blood is present I believe that an incision is preferable to the use of a needle or trocar. The use of these instruments was suggested in an article which appeared recently. The incision, it seems to me, is less likely to injure a coil of bowel should one happen to be in that area. The need for vaginal exploration has not impressed me greatly and I have not employed it in those cases which were handled by myself. Should one be in doubt, and desire to confirm the presence of a suspected ectopic pregnancy before proceeding to a fully developed operation, one may make a short incision low down in the mid-line of the abdomen. An inch in length suffices. This will at once prove the presence of free blood and, if this is found the incision may be quickly lengthened. It can be done with far less expenditure of time and with less chance of introducing infection into an area which is filled with blood than a colpotomy followed by laparotomy. If, in a clinic in which vaginal hysterectomy is frequently performed, only one ectopic in a series of this size is removed vaginally, it would not appear that the staff were impressed with the value of the vaginal pathway in dealing with this condition.

Appendectomy should not be done at the time operation is done for ectopic pregnancy. It is not wise to do any procedure involving surgery upon the intestine when the pelvis is filled with blood, an ideal culture medium. In the entire series it was done fourteen times. Only three of these were in the last group of seventy-four. In one case the operator frankly stated in his post-operative notes that there was "no particular indication." In one other case there had evidently been some pelvic inflammatory disease and a tubo-ovarian mass was adherent to the appendix. The present availability of the sulfonamide drugs and of penicillin should not influence the surgeon to assume risks which may be avoided. In the case in which the appendix was a part of a mass of which the pregnant tube also formed a part, the excision of the appendix may have been necessary. In other cases it would have been wiser to omit appendectomy. This should be the general rule.

In the first hundred cases hysterectomy was done seven times. The excision of the uterus was done for multiple fibroids in women past forty and when the condition of the patient rendered the additional procedure safe. In the last 74, small myomata were excised by myomectomy three times. This, also, may be done when the state of the patient is favorable but no additional operation should be done when blood loss to a dangerous degree has taken place. One hysterectomy was done in the second series of 74 in a woman who had an abdominal pregnancy with the placenta spread over the posterior surface of the uterus and broad ligaments. She was well past forty and it seemed the better way to

deal with the placenta. In the other case of abdominal pregnancy the placenta was not removed. This patient died on the table but her condition was very bad when the operation was begun. As a general rule it is better to leave the placenta in situ and to allow it to be absorbed. That this condition is still a dangerous one is indicated by the study of 236 cases in 1933 by Cornell and Lash who found a mortality of 14.3 per cent.

Inasmuch as patients with ectopic pregnancy are in their reproductive years it is wise to preserve the ovary if it is possible. The ovary was removed 37 times in the first hundred and 20 times in the last 74, making 57 cases in all in which it was sacrificed. If the patient is in serious condition it may be wiser to remove the adnexa on the affected side rapidly by mass ligatures but if her condition is not extremely serious it is possible by expenditure of only a small amount of extra time, to dissect off the tube, ligating bleeding points as they appear and to whip over the cut edge of the broad ligament with a fine suture. It should always be saved if practicable. Both tubes were removed only once in the second series. The exact number in the first series does not appear in the report but a statement is made that it is only done when the opposite tube showed changes sufficient to justify it.

We do not transfuse before operation unless the condition of the patient is extremely serious. Transfusion may be done while the operation is under way or, if blood is not immediately available, plasma may be used. While plasma is of tremendous value in emergencies there can be no question as to the greater value of whole blood when great loss of blood has occurred. One or more transfusions were given in 17 of the last group.

Operation is, as a rule, rather simple. The abdomen is opened, the affected tube quickly located, after which it is excised. In patients who are in serious condition, a clamp placed close to the uterus and one placed on the infundibulo-pelvic ligament outside the distal end of the tube will control the bleeding, after this the tube and ovary may be removed. In all others, the tube may be grasped close to the uterine horn while a second clamp, or Allis forceps, grasp the meso-salpinx just under the fimbriated end of the tube. One may get on without this latter instrument. The tube is then rapidly cut away with scissors cutting closely to the tubal wall. Bleeding points are caught as they appear. These are ligated, the small bit of tube held by the first clamp cut away together with a small wedge from the uterine horn and the cut edge of the broad ligament sewed over with fine surgical gut. The blood in the abdomen is not disturbed unless a part of it must be displaced to make it possible to see what one is doing. It is much better to leave it. The abdomen is then closed. Laparotomy packs are rarely needed. Many of these operations were done in twenty minutes or less. Speed and gentleness are both of real importance. A desperately sick woman will recover from a rapid and non-traumatic operation when she would succumb from a procedure carried out by a slow and hesitating operator.

The after-care is simple. Stimulants should not be used. Morphine is a tried remedy in the practice of medicine and it serves us well here, especially

the first twenty-four hours. Fluids are essential, especially blood in those whose blood loss has been great.

There were four deaths in this entire series. Three occurred in the first group and one in the second. One of those in the first group was brought to the hospital in a very serious condition. She was operated upon, transfused and seemed in very good condition the day after operation. She developed pneumonia shortly after the operation and subsequently died. Another death has already been alluded to. With a little more promptness in the recognition of her trouble the patient might have been saved. The death in the second series occurred in a case of abdominal pregnancy. One woman, during the period of time in which the second series of patients were cared for, came into the hospital with what seemed to be an ectopic pregnancy. She was not at the time in bad condition and refused operation. She left the hospital against advice. Shortly hereafter she entered another institution in a serious state and we were informed that she died during or immediately after operation.

Morbidity was not noted in the first series but 24 of the second group, or 32.4 per cent of this number, were morbid according to the usual standard, that is, a temperature of 100.4°F. on any two days excluding the first twenty-four hours.

Four deaths occurred in the entire series, a rate of 2.29 per cent.

#### CONCLUSIONS

1. Early recognition is important. The possibility of ectopic pregnancy in woman capable of pregnancy, should always be considered when lower abdominal pain appears.
2. Irregular bleeding is a very frequent symptom.
3. Curettage is not very helpful and, if used, its relationship to the length of time of bleeding must be considered.
4. Rapid and non-traumatic operative work is essential.
5. The exercise of good clinical judgment and the employment of skillful technique will give a high percentage of recoveries.

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## SPONTANEOUS VESICO-VAGINAL FISTULA IN A TUBERCULOUS BLADDER

### REPORT OF A CASE

LEO EDELMAN, M.D.

(New York, N. Y.)

*From the Urological Service of the Mount Sinai Hospital*

Spontaneous vesico-vaginal fistula is a rare complication in urinary tuberculosis. It occurred only once in our series of well over 500 cases of chronic renal tuberculosis observed during the past thirty-five years. The rarity of the complication and the favorable response to the type of treatment employed makes the case worthy of report.

*History.* (Adm. #519501) K. L., female, age 46, was readmitted to the Urological Service of the Mount Sinai Hospital on April 27, 1944 complaining of urinary incontinence. She had been a patient on the Service of the late Dr. Edwin Beer in August 1934 at which time a diagnosis of right renal tuberculosis was made and a right nephrectomy and partial ureterectomy was performed. Tubercle bacilli were recovered from the right kidney and bladder urine. The left kidney was normal and free of tubercle bacilli. She made an uneventful recovery and was symptom-free up to April 1938 when frequency and nocturia returned together with an occasional pain in the left kidney region. Intravenous pyelogram taken on May 14, 1938 showed a contracted bladder with moderate dilatation of the left renal pelvis suggestive of tubercular involvement of the remaining kidney. No tubercle bacilli were recovered from the urine. The frequency, nocturia, and dysuria persisted. The urine was repeatedly negative for tubercle bacilli. A check-up intravenous pyelogram in July 1940 showed a progression in the degree of hydronephrosis. Cystoscopy disclosed a diffusely inflamed bladder without demonstrable ulcerations. The urine was negative for tubercle bacilli. The patient moved out of town and failed to communicate with our follow-up department for approximately four years. She returned on February 7, 1944 stating that the frequency and nocturia persisted uninterruptedly but felt otherwise well. Cystoscopy showed a diffusely inflamed bladder with markedly diminished capacity. The left ureteral orifice was not visualized. The urine contained many pus cells, scattered red blood cells, and was negative for tubercle bacilli. A nephrostomy was advised because of the increased hydronephrosis with marked diminution in bladder capacity. The patient refused operation. The patient had no local treatment or instrumentation from February 7, 1944 to April 15, 1944 when she suddenly developed urinary incontinence and the constant urinary leakage forced her to seek relief.

*Examination.* On admission the physical examination was essentially negative except for the presence of an indurated area in the right anterior vaginal wall. With the aid of a vaginal speculum a fistulous opening could be seen to the right of the cervico-vaginal fold discharging urine. Indigo-stained fluid introduced into the bladder by catheter promptly appeared through the opening in the vagina. Cystoscopy showed the presence of a low grade cystitis with diminished bladder capacity and a fistulous opening corresponding to the site of the right ureteral orifice. This fistulous opening was catheterized and the catheter appeared in the vagina. The left orifice was not visualized.

*Laboratory data.* The urine obtained from the bladder contained numerous pus cells and was positive for tubercle bacilli. Hemolytic streptococci and streptococcus viridans were recovered from the urine on culture. The hemoglobin was 74 per cent, leucocyte count

7,100. The blood Wassermann was negative; blood urea nitrogen, 15 mg. per 100 cc. An x-ray of the chest was negative for tuberculosis.

Intravenous pyelogram showed an increase in the degree of hydronephrosis. The ureter was not visualized.

The history and clinical findings were fairly conclusive that we were dealing with a spontaneous vesico-vaginal fistula secondary to tuberculosis involving the remaining kidney.

*Operation.* A left nephrostomy was performed under cyclopropane ether anaesthesia on May 5, 1944. The kidney was found hydronephrotic but otherwise grossly normal. One hundred cc. of purulent urine was aspirated from the dilated pelvis and was positive for tubercle bacilli. Nephrostomy was performed in the lower pole with the aid of the Kimball hook passed through a small pyelotomy which was subsequently closed. The ureter was not ligated.

*Post-operative course.* Post-operative convalescence was uneventful, the patient leaving the hospital three weeks after operation, wound entirely healed, nephrostomy functioning well, and no recurrence of vaginal leak. She had gained weight, looked well, and felt fine. The nephrostomy tube has been changed approximately once every six weeks. When last seen on October 30, 1946, two and one half years after operation, she was in excellent condition.

#### DISCUSSION

Spontaneous bladder fistulae can occur from various causes, either by extension of disease from without or from the diseased bladder wall itself. This discussion will be limited only to spontaneous perforation associated with urinary tuberculosis.

The subject was admirably reviewed by Mertz (1) in 1933 on the basis of twenty-nine cases collected from the literature to which he added one case. Twelve of the cases were clinical studies, fourteen were autopsy findings and in four the source was indefinite.

In twelve of the cases perforation occurred in the vertex of the bladder and in fourteen in the base. In the first group, one half communicated with the peritoneal cavity and the remaining one half drained into the prevesical space. Of those penetrating the base, only six opened into the vagina. Braasch (2) observed several instances of vesico-vaginal fistula in patients in whom a tuberculous kidney was removed several years before. He is of the opinion that bladder tuberculosis can persist for several years after removal of a tuberculous kidney, the remaining kidney being normal. Crowell (3) cited a similar case, the perforation occurring three years after nephrectomy. Wyatt and Douglass (4) in 1938 reported a case of spontaneous vesico-vaginal fistula, the only one in their series at the Vanderbilt University Hospital.

It is not entirely clear why perforation takes place in bladder tuberculosis. Mertz, based on his studies of the cases in the literature, concludes that "it is not the actual extension of the tuberculosis itself through the bladder," but that "a bacterial thrombus forms in a tuberculous ulceration and that the perforation is due to mixed infection, rather than to the tubercle germ itself." Halle and Motz (5), and Walker (6) indicate that in the destructive stages of vesical tuberculosis tubercle bacilli or tubercles may or may not be found in the tissues.



The symptoms of perforation are dependent on the site of drainage. The actual perforation is not painful and may or may not be preceded by an aggravation of urinary symptoms.

Communication with the vagina results in a constant vaginal urinary leak with cessation of the desire to void.

Perforation into the prevesical tissues, according to Caulk (7) is accompanied by severe pain at the site of drainage, vomiting, and shock. There is increased bladder irritability, frequency, urgency, tenesmus, and only small amounts of urine are voided. Catheterization does not afford relief and only a small amount of bloody urine is recovered from the bladder. Local pain and swelling appear early, gradually increase and if untreated, are followed by symptoms of sepsis.

Intra-peritoneal communication is accompanied by sudden severe, acute, abdominal pain followed by signs and symptoms of a rapidly spreading peritonitis. The patient passes very little urine, and usually nothing is obtained by catheter. Failure to recover fluid introduced into the bladder or an aero-cystogram are helpful diagnostic aids.

The treatment for vesico-vaginal fistula is dependent upon the patient's local and general condition. When only one kidney is involved, as in the case reported by Wyatt and Douglass, nephrectomy resulted in a cure. When dealing with a solitary kidney, one must resort to nephrostomy or ureteral transplantation. Attempts at repair of the fistula have proven unsuccessful in all reported cases. When the solitary kidney is hydronephrotic, we believe nephrostomy is preferable to ureterostomy or ureteral transplantation. Ligation of the ureter is not essential. Retaining the continuity of the ureter has a good psychological effect on the patient and does not interfere with the desired result.

Prompt drainage of the bladder and the resulting abscess is indicated when perforation takes place into the prevesical tissues. A persistent urinary fistula may require ureteral ligation and nephrostomy when dealing with a solitary kidney.

Intraperitoneal perforations have been uniformly fatal. The only hope is prompt and adequate suprapubic drainage of the bladder with protection of the peritoneal cavity.

#### SUMMARY

A case of spontaneous tuberculous vesico-vaginal fistula is recorded. It is the only such instance in our series of well over five hundred cases of renal tuberculosis. The condition developed ten years after nephrectomy for unilateral renal tuberculosis or six years after involvement of the remaining kidney. Nephrostomy without ureteral ligation has kept the patient comfortable and well for the past two and one half years.

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## AN ANALYSIS OF 529 CONSECUTIVE CESAREAN SECTIONS

MORRIS FERESTEN, M.D., F.A.C.S

(Fall River, Massachusetts)

*From the Department of Obstetrics, Union Hospital*

Despite recent advances in obstetrics, cesarean section still remains a much abused procedure, with a high maternal and infant mortality rate. Statistics repeatedly show that it is not the simple and safe procedure it is popularly believed to be. When properly indicated, abdominal delivery is often a life saving measure for both mother and child. The results of cesarean section, however, compare so unfavorably with those of vaginal delivery, that the latter procedure must always be the method of choice, whenever possible. It is fitting that statistics bearing on these matters continue to be published for study and constructive criticism.

In the present paper, a critical analysis has been made of 529 consecutive cesarean sections, performed at the Union Hospital from January 1, 1936 to the end of June, 1946. These women were operated upon by 14 physicians, and for the most part were private patients of well qualified obstetricians.

### INCIDENCE

In the ten and a half year period covered in this paper, there were 6895 confinements. Five hundred and twenty-nine of these patients, or 7.67 per cent, were delivered by cesarean section. This incidence is high as compared to the 2.1 per cent proportion of abdominal deliveries in the series of Kohn, Morrison and Douglass (1). However, Thoms and Godfried (2) reported an incidence of 3.2 per cent cesarean sections in their ward cases, as compared to 9.6 per cent in their private series. As they point out, this higher incidence in private patients, such as those analysed here, is primarily due to the referral of complicated obstetric cases to a specialist. Patients, too, who have had previous obstetric difficulties, will frequently consult a specialist for subsequent delivery.

In Table I, the incidence of the various types of cesarean section is listed for each year. When we take into consideration the cumulative number of repeat operations, we find that there has been a constant decrease in initial cesarean sections.

Most of the elective cesarean sections were performed by the classical method. The cervical cesarean operation was reserved for those patients who had been in labor, particularly for those with ruptured membranes. There were 37 Porro operations in this series. This procedure was found particularly successful in the severely infected cases. The sulfonamides and penicillin have been found to be invaluable aids in combating infection.

### INDICATIONS

The indications for cesarean section are shown in Table II.

The 133 patients who had a repeat abdominal delivery were excluded from this consideration. The obstetricians of the Union Hospital favored the dictum

"once a cesarean, always a cesarean." The good results of Duckering (3) who reported a series in which 42 per cent of a group of patients with a previous cesarean section were delivered by the vaginal route subsequently, might well

TABLE I

*Incidence*

YEAR	TOTAL DELIVERIES	CLASSICAL CESAREANS	CERVICAL CESAREANS	PORRO OPERATIONS	TOTAL	INCIDENCE
1936	433	41	8	3	52	12.01%
1937	443	26	12	3	41	9.25%
1938	452	26	9	6	41	9.07%
1939	511	46	5	4	55	10.76%
1940	543	29	9	4	42	7.73%
1941	646	26	13	3	42	6.50%
1942	826	38	9	2	49	5.93%
1943	898	44	4	3	51	5.68%
1944	830	49	5	6	60	7.23%
1945	882	65	7	2	74	8.39%
1946	431	16	5	1	22	5.10%
Total...	6895	406	86	37	529	7.67%

TABLE II

*Indications*

INDICATIONS	CASES	PER CENT
Cephalopelvic disproportion.....	208	52.52
Toxemia of pregnancy.....	36	9.09
Placenta previa.....	28	7.07
Abruptio placentae.....	25	6.32
Cardiac disease.....	19	4.79
Elderly primigravida.....	17	4.29
Myomata uteri.....	13	3.28
Uterine inertia.....	12	3.03
Previous plastic repair.....	11	2.78
Sterility.....	10	2.53
Transverse presentation.....	10	2.53
Obstructing ovarian cyst.....	4	1.01
Tuberculosis.....	3	.76
Total.....	396	100.00

encourage a more common recourse to this practice. Selected patients, who have had abnormalities such as pre-eclampsia and abnormal presentations which are not likely to be present in succeeding pregnancies, might cautiously be allowed to deliver vaginally.

The most common indication was cephalopelvic disproportion, accounting for 52 per cent of the cesarean sections. A more frequent recourse to x-ray

mensuration, the Hillis maneuver at term, and an adequate trial of labor for patients with a borderline pelvis, would undoubtedly have reduced the number of abdominal deliveries. The toxemias consisted of patients in severe pre-eclampsia, who did not respond to active therapy. The two hemorrhagic complications of the last trimester of pregnancy, placenta previa and abruptio placentae, accounted for 13.39 per cent of the series. A high valuation of the baby for the elderly primipara, and for patients who had had several miscarriages or stillbirths, often with an incompatible Rh factor, comprised a justifiable 6.82 per cent. The indication for cesarean section in the 19 cardiac cases was made by an internist, after careful study of the patients. Eleven women were delivered by the abdominal route because of a previous plastic repair of the genital tract. Frequently, it is preferable to defer a vaginal operation until the patient has had the desired number of children.

#### DURATION OF LABOR

Three hundred and forty-nine patients, or 65.97 per cent, had not been in labor. An elective operation was performed for the majority of these women. A previous cesarean section accounted for 118 cases in this category. Seventy-seven of the 208 patients operated upon for cephalopelvic disproportion, or 37.02 per cent, had not been in labor. The addition of chemotherapy may well justify a more liberal attitude towards a trial of labor in borderline cases. The remainder of this group comprised the patients with pre-eclampsia, cardiac disease, hemorrhage in the last trimester, the elective cases with previous miscarriages, stillbirths, and the elderly primigravida.

The duration of labor is shown in Table III.

Only 14 patients, or 2.65 per cent, were in labor over 24 hours at the time the cesarean section was performed.

#### CONDITION OF MEMBRANES

Four hundred and forty-two patients, or 83.55 per cent, had intact membranes at the time of operation. Only 31 patients, or 5.86 per cent, had membranes ruptured over 24 hours. The interval which elapsed from the time of rupture of membranes and operation was less than 12 hours in the remaining 56 cases (10.59 per cent).

#### ANESTHESIA

The types of anesthesia employed in this series are shown in Table IV.

Gas-oxygen-ether was the agent employed for 87.52 per cent of the cesarean sections.

Fourteen patients were satisfactorily anesthetized with intravenous sodium pentothal. It is to be remembered that this anesthetic is contra-indicated in the presence of shock. If used at all, it should be reserved for the elective case in good physical condition.

Spinal anesthesia was employed for 33 cesarean section. It may have contributed to one maternal death in a patient with abruptio placentae. Greenhill



(4) states that sudden death from excessive lowering of the blood pressure or depression of the respiratory center, and the many other sequelae reported in the literature, make spinal anesthesia a most hazardous anesthetic for the pregnant woman.

Local anesthesia was employed in only 3 cases. Unfortunately, the mental attitude of the Latin patient, so often encountered in this series, made the use

TABLE III  
*Duration of Labor*

	CASES	PER CENT
Not in labor.....	349	65.97
In labor.....		
less than 6 hours.....	15	2.84
6 to 12 hours.....	60	11.34
12 to 24 hours.....	91	17.20
24 to 36 hours.....	11	2.08
36 to 48 hours.....	1	.19
over 48 hours.....	2	.38
Total.....	529	100.00

TABLE IV  
*Anesthetic*

	CASES	PER CENT
Gas-oxygen-ether.....	463	87.52
Spinal.....	33	6.24
Cyclopropane.....	16	3.03
Sodium pentothal, intravenously.....	14	2.64
Local novocaine.....	3	.57
Total.....	529	100.00

of this ideal anesthetic difficult. Then too, the technic though simple requires a great deal of patience, which is usually lacking in the busy obstetrician.

#### PORRO OPERATION

Supravaginal amputation of the uterus, after removal of the fetus, was performed 37 times for the indications shown in Table V.

The Porro operation was done to reduce the risk of hemorrhage and sepsis in 8 cases with ruptured uteri, in 12 cases with fibroids, and in 2 cases of neglected cephalopelvic disproportion.

The Porro operation was performed to control the severe hemorrhage of 5 patients with abruptio placentae and of one patient with a placenta previa.

Nine women with severe constitutional disease were sterilized by hysterectomy.

The eight patients with ruptured uteri had had a previous classical cesarean section. All of them recovered. The low cervical technic might have prevented this complication, although I have had one case with a ruptured uterine incision following the low cervical operation.

#### MORBIDITY

One hundred and forty-six patients, or 27.59 per cent, had a temperature elevation to 100.4°F., or more during two 24 hour periods after operation.

TABLE V  
*Porro Operations*

INDICATIONS	CASES	PER CENT
Fibromyomata uteri.....	12	32.43
Sterilization for constitutional disease.....	9	24.33
Ruptured uterus.....	8	21.62
Abruptio placentae.....	5	13.51
Cephalopelvic disproportion.....	2	5.41
Placenta previa.....	1	2.70
Total.....	37	100.00

TABLE VI  
*Cause of Morbidity*

CAUSE OF MORBIDITY	CASES	PER CENT
Sapremia.....	47	42.73
Upper respiratory infection.....	20	18.18
Infected wound.....	15	13.63
Thrombophlebitis.....	14	12.73
Peritonitis.....	7	6.36
Pyelitis.....	5	4.55
Breast abscess.....	1	.91
Pelvic abscess.....	1	.91
Total.....	110	100.00

The lowest morbidity rate was present in the group of 406 patients who had had classical cesarean sections, most of which were performed for elective indications. One hundred and eight of these women, or 26.60 per cent, ran a febrile course.

Eleven of the 37 patients who had had the Porro operation, or 29.72 per cent, showed a temperature elevation for two or more days.

Twenty-seven of the 86 patients who had had a cervical cesarean section, or 31.39 per cent, ran a morbid course. This high incidence is probably due to the fact that laparotrachelotomy was the operation reserved for the patients who had been in labor for considerable time, often with ruptured membranes, and

potentially infected. Had this type of operation been performed in the elective cases, the morbidity rate would undoubtedly have been much lower. As Phaneuf (5) has emphasized so many times, the cervical cesarean section offers better protection against septic peritonitis, better healing of the incision, and an easier convalescence.

In 36 cases no cause could be found for the elevation of temperature. The cause of fever in the remaining 110 cases is shown in Table VI.

All but one of the seven patients with peritonitis recovered after a stormy convalescence. The 47 women with sapremia and lochimetra ran a mild febrile course. The remaining 56 patients quickly responded to appropriate therapy.

In recent years, the routine intraperitoneal use of sulfanilamide crystals has resulted in a definite decrease in the morbidity rate.

#### INFANT MORTALITY

Thirty-two babies, or 6.05 per cent of the series, were stillborn or died within two days after operation. This high rate again reveals the fallacy of the belief that the babies have a better chance for life with cesarean section.

Four of the stillbirths were due to congenital deformities incompatible with life. In 9 instances of abruptio placentae and in one case of placenta previa, apnea resulted from mechanical interference with the placental circulation. Eight babies died of prematurity. The remaining 10 infant deaths occurred in patients who had had an elective cesarean section. Since none of these babies were autopsied, the exact cause of death was not determined.

Russ and Strong (6) remind us that the average baby born from a cesarean section does not breathe as spontaneously or as quickly as a baby delivered by other methods. They believe that the squeezing action on the lungs and head, produced by the passage through the normal birth channel, is probably the major stimulus for the baby to breathe. They emphasize the value of intratracheal catheterization, and report a decline in the infant mortality rate from 8.7 per cent to 1.8 per cent when this procedure was carried out routinely.

#### MATERNAL MORTALITY

There were seven deaths in this series, giving a maternal mortality rate of 1.32 per cent. W. J. Dieckmann (7) believes the maximum mortality rate for cesarean section should be 0.5 to 1 per cent. He states that in the treatment of contracted pelvis, elective operation should have a maximum mortality of 0.2 per cent and after a test of labor 0.4 per cent. In this series there were no maternal deaths when the cesarean section was performed as an elective operation before labor began. The classical procedure was usually selected for this group.

A brief summary of the seven deaths follows.

*Case 1.* Mrs. B., para VII, 40 years of age, had a classical cesarean section performed under gas-oxygen-ether anesthesia, August 2, 1936. She had had two severe hemorrhages the day before admission, and was advised to rest in bed by her family physician. On admission, she was bleeding profusely. Her blood pressure was 70 systolic, 50 diastolic.

At operation, she was found to have a complete placenta previa. A transfusion of 500 c.c. of blood was given following the section. The patient died 45 minutes after operation from shock and hemorrhage. The baby was stillborn.

*Case 2.* Mrs. T., para I, 35 years of age, was operated upon January 15, 1937, in the seventh month of pregnancy. She had been hospitalized for two months with cardiac decompensation. A classical cesarean section was done under gas-oxygen-ether anesthesia, on the advice of a cardiologist. The patient died while the skin was being closed. Autopsy showed mitral stenosis, myocarditis, and congestion of the lungs, liver and kidneys. The baby was stillborn.

*Case 3.* Mrs. P., 40 years of age, a primipara, was operated upon April 3, 1937. For two weeks she had been having irregular labor pains, ran a mild febrile course, and refused hospitalization. On admission, the cervix was two centimeters dilated and emitted a profuse foul discharge. There was an obstructing fibroid, the size of a grapefruit filling the cul de sac. A Porro operation was performed under gas oxygen ether. The fibroid was markedly degenerated. The patient was given prontosil intravenously. She died five days after operation. Autopsy showed a general peritonitis. The baby was stillborn.

*Case 4.* Mrs. W., a primipara, 30 years of age, was operated upon June 13, 1940. She had a platypelloid type of pelvis, and was given a 12 hour trial of labor. At operation, the membranes were intact and the head was unengaged. A low cervical cesarean section was performed under gas-oxygen-ether anesthesia. She bled profusely after operation, and was given glucose and coramine intravenously. She died four hours after operation from shock and hemorrhage. The baby lived.

*Case 5.* Mrs. L., 33 years of age, para IX, was operated upon January 5, 1941, three weeks before the expected date of delivery. She had been hospitalized for two months with a diagnosis of placenta previa, confirmed by x-ray. During this period, she had bled mildly on several occasions. A classical cesarean section was done under gas-oxygen-ether anesthesia. After operation, the patient bled profusely, and was given two transfusions of 500 c.c. of blood. She died 8½ hours after operation from shock and hemorrhage. The baby lived.

*Case 6.* Mrs. C., 29 years of age, a primipara, was operated upon February 18, 1941, for abruptio placentae. A low cervical cesarean section was done under spinal anesthesia. The placenta was found free in the uterine cavity. The uterus was a typical Couvelaire type. Unfortunately it was not removed. The patient continued to bleed and died 10 hours after operation from shock and hemorrhage. The baby was stillborn.

*Case 7.* Mrs. F., 39 years of age, para II, was operated upon August 21, 1945, in the sixth month of pregnancy. She had been bleeding moderately for four days. A low cervical cesarean section was done under gas-oxygen-ether anesthesia for abruptio placentae. The uterus did not contract well. She continued to bleed, and was given a transfusion of 500 c.c. of blood. She died in circulatory collapse from shock and hemorrhage, three days after operation. The baby was stillborn.

Five of the maternal deaths resulted from shock and hemorrhage. A freer access to blood in a blood bank, allowing for earlier large transfusions, might have saved some of these patients.

Packing the uterus at the time of operation is often a life saving procedure in cases of hemorrhage, and should be resorted to more frequently.

The two patients with abruptio placentae might have fared better after a hysterectomy. However, this is often a difficult decision to make.

Spinal anesthesia was contra-indicated in Case 6., in the presence of shock and hemorrhage.

Local anesthesia would have been preferable for the patient with mitral stenosis.

Cases 1 and 3, neglected before admission, illustrate the harm that can be done to an unsuspecting patient by a poorly informed family physician.

#### SUMMARY AND CONCLUSIONS

1. There were 529 cesarean sections performed at the Union Hospital, Fall River, Mass., from January 1, 1936 to the end of June, 1946; an incidence of 7.67 per cent of all deliveries.

2. The most common indication for abdominal delivery was cephalopelvic disproportion, accounting for 52.52 per cent of this series. A more frequent resort to x-ray mensuration, the Hillis maneuver at term, and an adequate trial of labor for the patient with a borderline pelvis, would undoubtedly have allowed some of these women to have delivered through the vaginal route.

3. One hundred and thirty-three patients had repeat cesarean sections. Some of these women, who no longer had abnormalities for which the original operation was performed, might possibly have been delivered vaginally.

4. Three hundred and forty-nine patients, or 65.97 per cent had not been in labor. Only fourteen women, or 2.65 per cent, were in labor over 24 hours.

5. Eighty-seven patients, or 16.45 per cent, had ruptured membranes.

6. Gas-oxygen-ether was the anesthetic employed in 87.52 per cent of the cases. Local infiltration, the ideal anesthetic, was used only 3 times. Intravenous sodium pentothal was employed in 14 cases. Thirty-three patients, or 6.24 per cent, had spinal anesthesia. The spinal novocaine may have contributed to the death of one woman with an abruptio placentae, who died from shock and hemorrhage.

7. Supravaginal amputation of the uterus, after removal of the fetus, was performed 37 times. It was the procedure selected to reduce the risk from hemorrhage and sepsis in 8 cases of ruptured uteri following a classical cesarean section, in 12 cases of fibroids, and in 2 cases of neglected cephalopelvic disproportion. The uteri of 5 patients with abruptio placentae, and of one with a placenta previa, were removed to control severe hemorrhage. The Porro operation was employed to sterilize 9 women with severe constitutional disease.

8. One hundred and forty-six women, or 27.59 per cent, had a temperature elevation to 100.4°F., or more, during two 24 hour periods after operation. The lowest morbidity rate, 26.60 per cent, was present in the group of 406 patients who had had the classical type of operation. Most of these women had had an elective cesarean section performed without a trial of labor. Sepsis with lochiometra was the most common cause of morbidity.

9. Thirty-two babies, or 6.05 per cent, were stillborn or died within two days of birth. Four of the deaths were due to congenital deformities incompatible with life. In nine instances of abruptio placentae and in one case of placenta previa, asphyxia resulted from mechanical interference with the placental circulation. Eight babies died of prematurity. Ten women who had had an elective cesarean section had stillbirths. Local anesthesia might have saved some of these babies.

10. There were seven maternal deaths, presenting a mortality rate of 1.32 per



cent. There were no deaths in the large group of elective cesarean sections performed without a trial of labor. Shock and hemorrhage were the cause of death of two women with abruptio placentae, of two others with placenta previa, and of one patient with cephalopelvic disproportion. One patient with mitral stenosis died at operation of heart failure. One patient with an obstructing degenerated fibroid died of general peritonitis.

11. A freer access to large quantities of blood in a blood bank, local anesthesia, the use of intrauterine packing, and the removal of the Couvelaire type of uterus, might possibly have saved some of the patients who died from shock and hemorrhage. Education of the general practitioner to the dangers of uterine bleeding in the last trimester of pregnancy will hasten adequate treatment, and would have saved at least one patient in this series.

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## STERILITY

### PERSONAL OBSERVATIONS

ROBERT THRIFT FERGUSON, M.D.

(Charlotte, N. C.)

I feel quite honored on having been invited to contribute an article for publication in the special number of the Journal of the Mount Sinai Hospital honoring Dr. I. C. Rubin. I feel sure that I would never have done the work which I am reporting here had it not been for the stimulus offered by Dr. Rubin in his monumental work of injecting oxygen into the peritoneal cavity. Having been interested in sterility, and having read Dr. Rubin's article describing his work, I immediately went to New York to see him at work. On my way home I thought much about his method and how it might be simplified. My first step on returning to my laboratory was to make the tube with which I have performed all my tests (fig. 1).

My apparatus was described in *Surgery, Gynecology and Obstetrics* in 1924 and it was so well received here and abroad that I had letters of inquiry from more than 30 states in the United States and many foreign countries including Russia. This encouraged me to carry on my work, quite successfully, up to the present time, reporting my results in a number of articles (1). I feel that another report on 1000 patients merits presentation and I am happy to do so in honor of Dr. Rubin. In my work I have used unsterilized air in the place of oxygen and I think the results reported herewith will be conclusive of its efficiency.

The method of preparing a patient for the tubal patency test has been published so often that it would be superfluous to repeat it here. In my experience the normal tube should be patent at a pressure of around 40 mm. Hg, but I have discovered that if the patency does not occur until a pressure of 200 mm. Hg has been reached the patient will frequently conceive. I have never carried the pressure above 200 for fear of rupturing the tubes. Having had no misfortune at this pressure I have adopted this as my limit. I have never felt satisfied with one test and do repeated tests on those who do not conceive following the first test. In following this rule I have had many patients to conceive later on and I have performed the test at an average of four times each on the 1000 patients to be reported here.

The usual precautions are taken to see that the patient has no vaginal infection which might cause the germs to be forced through the tubes into the peritoneal cavity with a resulting peritonitis. Neither have I had a patient to develop endometriosis afterwards. Only one morbidity has occurred in this series, and this was in the early days of my work in a patient who had no leukorrhea and no vaginal symptoms. Four days later she developed an acute gonorrheal salpingitis, proved by finding the Neisserian bacillus in the cultures. This disabled her and kept her in bed for two weeks. It also put me on my guard and I have had no further morbidity.

In the accompanying Table I have collected my several observations and shall comment briefly on the more important ones.

I do not see many patients with Neisserian infection, but multitudes of them give a history of having had the infection. I see many sterile women whose history is definitely that of a previous gonorrheal infection. Since the advent of the



FIG. 1

Sulfa drugs and penicillin such patients do not develop salpingitis, and are therefore prevented from developing sterility.

Cervicitis and endocervicitis are extremely common, and the type who has a tenacious ropy discharge exuding from the cervix will frequently conceive following cauterization or conization of the cervix.

Miscarriages have a definite bearing on sterility and many of my patients with secondary sterility have remained so following miscarriage or abortion. With those who have had infections following it is easily explainable but with

the remainder it is hard to determine the cause. Twenty per cent of this series have had a dilatation and curettage for sterility before coming tome. These

TABLE I

Average age.....	30
Average menstrual age.....	13
No. of years married.....	6
Average blood pressure.....	110/72
Headache.....	57%
Backache.....	61%
Dysmenorrhea.....	62%
Painful coitus.....	10%
Constipation.....	48%
Hemorrhoids.....	3%
Passing clots at periods.....	52%
Having had tonsils removed.....	54%
White blood count above 10,000.....	13%
Red blood cell count below 4 million.....	25%
Heart disease.....	1.75%
Tuberculosis in any form.....	1.25%
Fistula in ano.....	1.25%
Neisserian infection (proved).....	2.8%
Syphilis.....	4%
Abscess in Bartholin's gland.....	2.3%
Leukorrhea.....	45%
Percentage of these leukorrheas caused by Trichomonas infection.....	30%
Polyps.....	2.3%
Having previously worn pessaries.....	6.8%
Cystic ovaries.....	11.5%
Fibroid tumors of the uterus.....	4%
Malposition of the uterus.....	33%
Previous ectopic.....	.6%
Cervicitis and endocervicitis.....	25%
Previous miscarriages.....	16.5%
Former curettage.....	20%
Previous pelvic operations.....	37.5%
One or more pregnancies.....	27.5%
Albumen in urine.....	1.6%
Sugar in urine.....	.5%
Sterile husbands.....	2.6%
Operated on by me.....	16.5%
Patent tubes.....	39.8%
Non patent tubes.....	60.2%
Pregnancy after test in 1000 patients.....	13.3%
Pregnancy after test in those whose tubes were patent.....	35.75%
Pregnancy after test in married women whose tubes were patent.....	50%
(33 of the thousand patients were single)	
Average number of tests per patient.....	4

had never had a tubal patency test done, and I cannot understand why any physician in this day and time would perform a curettage on a patient for sterility unless and until the tubes had been tested for patency. An operation of this

character for sterility on a patient with non-patent tubes is unthinkable. Many patients seem to be sterile following any type of abdominal operation and I think this is often due to pelvic adhesions.

When I have a patient come in for sterility and find her tubes patent, and the patient normal in every other respect, then I have the husband examined for sterility, and I have been very much surprised at the very small number of sterile men. The unfortunate thing is that so many men will tell you that they have had gonorrhea and they are perfectly potent while their wives have become sterile following infection by the husband.

Plastic operations on the tubes for sterility, in my hands, have been successful in a small percentage, and I never advise it unless I can find definite pathology, and then only after explaining to the patient that the chances of conception are not more than 8 per cent.

In this series practically 40 per cent of the patients were found to have patent tubes and 60 per cent nonpatent. This includes those who have come in for diagnosis and the tubal test was done to make sure of the diagnosis in a number of them. I have found in those who have come primarily for sterility that 45 per cent were patent and 55 per cent nonpatent. A few of these had the tubes tested on account of dysmenorrhea. I found that a number of patients who had been tested for sterility had reported that the dysmenorrhea had been relieved for a period of one to several months following the test and this led me to try it on some of the young women suffering only from dysmenorrhea, and with marked success in several of them.

Of the 1000 tested for sterility, diagnosis and dysmenorrhea, 13.3 per cent conceived following the test. Out of those whose tubes were patent, 35.75 per cent became pregnant, and of the married women alone whose tubes were patent 50 per cent conceived, and it was interesting that a number of them conceived before the next period. Out of 100 women in a previous report by me 85.7 per cent of those who had patent tubes became pregnant following the test.

In the past when reporting a series of patients on whom I had performed the test I wrote them a letter asking if they had conceived following the test, and enclosed a self addressed post card asking them to merely say "yes" or "no" but only a small number would take the trouble to reply, so I have given up this method. I am satisfied that the percentage of conceptions following the test would be much greater than reported here had I any way of following up the patients.

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## POLYCYSTIC KIDNEY DISEASE IN PREGNANCY

PALMER FINDLEY, M. D.

(Omaha, Nebraska)

Polycystic kidneys are not of extreme rarity as judged from a review of the urological literature, yet few cases of pregnancy associated with the disease are on record. Why this is so is not clear, as polycystic kidney disease is most frequently recognized in the child bearing period.

It is not my purpose to stress the urological aspects of the problem. Suffice it to say that there seems to be no consensus among urologists as to the etiology of polycystic kidneys. All agree that the lesion is congenital and bilateral, that it is progressive to the extent of ultimately destroying the kidney structure and that the cysts are the result of a developmental obstruction at some point along the course of the uriniferous tubules. The exact site and nature of the developmental fault is not clearly defined.

The life expectancy from the time of recognition of the lesion is seldom more than ten to fifteen years, though in a few instances old age has been attained. Death due to uremia is the usual result. There is no evidence that pregnancy accelerates the development of cysts in the kidney.

Since it is agreed that polycystic kidneys are hereditary in a large proportion of cases it is pertinent to inquire whether a woman with polycystic kidneys should bear children. It is my belief that they should not—this in the interest of both mother and child.

Polycystic kidneys may be and often are overlooked. This is particularly true in the second semester of pregnancy when the swollen kidneys are difficult to outline apart from the gravid uterus. In the absence of a pyelogram the diagnosis of toxemia is commonly made. Where the kidneys are greatly enlarged and particularly in the presence of abscesses in the kidney, as in the case here recorded, the interruption of the pregnancy may become imperative and may not be delayed to the period of viability.

Because of the progressive nature of the lesion and because both kidneys are invariably involved, though seldom to the same degree, nephrectomy should seldom if ever be resorted to. Drainage of large cysts and abscesses affords temporary relief. Obstructing stones occasionally demand surgical intervention.

### CASE REPORT

*History.* Mrs. X., aged 23 years, was in the twelfth week of her first pregnancy when first seen on January 10, 1945. For a period of one year she had suffered increasingly from pain in the left lumbar region, together with repeated attacks of abdominal pain lasting two to three weeks and accompanied by temperatures ranging from 101° to 105°F. At all times there was a feeling of general lassitude.

*Examination.* Cystoscopic examination and retrograde pyelography (Dr. Payson Adams) included the following salient points. The interior of the bladder appeared normal in all respects. Number 6 x-ray catheters passed readily to each renal pelvis and a clear flow of urine from each side was obtained. One cc. of phenolsulphthalein injected intra-

venously appeared on the right side in seven minutes and on the left side in six minutes. The specimen was collected for ten minutes after appearance time.

*Laboratory data.* The blood findings on admission to the hospital were: white blood cells, 5,000; red blood cells, 3,720,000; hemoglobin, 75 per cent. The urinalysis revealed a heavy deposit of pus cells, 2 plus albumin, no casts, no blood. Bladder urine revealed occasional white blood cells and many epithelial cells. Right kidney urine revealed 6 to 10 white blood cells; occasional epithelial cells; phenolsulphthalein total, 2 per cent in 10 minutes. Left kidney urine showed 1 to 3 white blood cells; occasional epithelial cells; phenolsulphthalein total, 1.5 per cent in 10 minutes; non-protein nitrogen, 32 mg. per cent.

*Course.* A film was taken with catheters in position after which a bilateral pyeloureterogram was obtained with approximately 7 cc. of skiadam injected on the left side causing a little pain in the left flank, and 7 cc. on the right side. Ureterograms were obtained by injecting the catheters during their withdrawal. The pyeloureterograms showed the upper third of the right ureter deflected medially perhaps by a large cyst of the lower pole of the right kidney which also elevated the lower calyx and lower part of the renal pelvis. The calyces on the right side otherwise appeared normal. The superior calyx on the left side was short and the inferior calyx was excessively long as compared with the upper calyx but there was no special filling defect on this side and the pelvis was normal. There was no shadow to indicate calculus in the urinary tract. On the whole these films were not as satisfactory as one would like because of poor exposure and the presence of intestinal gas.

Because of persistent fever, sepsis, pain in left flanks, and mounting nonprotein nitrogen during the following three weeks, the left kidney was explored by Dr. Adams. The following results were recorded by him:

"Left loin incision about 4 inches in length below the 12th rib, preserving the 12th nerve and ilioinguinal and iliohypogastric nerves. Perinephritic space opened and immediately on introducing the index finger anteriorly, a gush of pus appeared and on further inspection this was found to be coming from a large cavity in the kidney substance on the anterior lateral surface. The kidney was a huge affair—at least 5 times normal size—the lower pole extending well below the iliac crest and the upper pole elevating the diaphragm several inches. The surface of the kidney was rather smooth, thin-walled, and through the surface a number of cystic cavities could be seen but could not be felt satisfactorily. Those that could be seen were incised. Some of the cysts contained clear straw colored fluid and others contained purulent material. Several other large cavities were opened and drained of pus. The kidney was not completely mobilized on the anterior medial surfaces or at either pole. Four penrose drains were placed in the wound, brought out the posterior angle and the wound was closed with interrupted chromic sutures."

Before closure it was noted that the patient was not in good condition, the pulse was considerably elevated and it was thought undesirable to contemplate nephrectomy at this time. She was returned to her room and immediately given 250 cc. of blood by transfusion together with intravenous fluids.

The operation thus consisted of exploration of left kidney, multiple punctures of both infected and non-infected cysts.

In the presence of multiple abscess in the kidney, a kidney that was about five times normal in size, it was evident that the encroachment of the pregnant uterus would create an intolerable condition, hence my decision to terminate the pregnancy and excise the tubes to insure no future pregnancies. This was done by performing an abdominal hysterectomy, together with the severing of either tube from the uterine cornua. Following this procedure the patient made marked improvement. In two weeks the patient left the hospital, awaiting further developments.

#### CONCLUSIONS

1. Polycystic kidneys are associated with pregnancy more often than is generally recognized. This is so because of the difficulty in palpating the swollen

kidneys in advanced pregnancy. For the want of a pyelogram the diagnosis of toxemia is often made.

2. Pregnancy does not accelerate the development of the cysts in the kidney.

3. Drainage of large cysts in the kidney, of abscesses and the removal of ureteral stone may demand surgical interference but it is questionable if nephrectomy is ever justified.

4. The interruption of pregnancy before or after the period of viability is justified as a palliative procedure only when it becomes evident that the encroaching gravid uterus is creating an intolerable condition.

## SIMULATION OF MYOCARDIAL INFARCTION BY ESOPHAGEAL TEAR

ARTHUR M. FISHBERG, M.D.

(New York, N. Y.)

In view of the proximity of the two organs, it is not surprising, and has long been known that pain engendered in the esophagus may simulate cardiac pain. There is evidence (1) that distention of a diverticulum of the esophagus may produce anginal pain through reflex coronary constriction. That paraesophageal hiatus hernia may masquerade as angina is well known. Because of the frequency with which anginal patients state that eructation relieves their pain, the theory was advanced that anginal pain is due to esophageal spasm. Untenable as this suggestion is, clinical situations occur in which there is difficulty in differentiating cardiac and esophageal disease. This dilemma arises because, on the one hand, pain in malignant or other disease of the esophagus may simulate the substernal distress of angina and, on the other hand, dysphagia occasionally occurs in heart disease.

In this paper are described two instances of tear of the esophagus in which the diagnosis of myocardial infarction came into serious consideration.

### CASE REPORTS

*Case 1.* A previously healthy thirty-nine year old man consulted Dr. Sidney K. Apfel in 1941 for postprandial epigastric pain and heart burn. There was no dysphagia. X-ray examination of the alimentary tract revealed a smooth filling defect in the lower end of the esophagus. Esophagoscopy by Dr. Rudolph Kramer disclosed two small lesions about 34 and 35 centimeters from the incisor teeth; they were regarded as fibrolipomas.

Except for occasional heart burn, the patient felt well until New Year's Eve of 1945. That evening he had numerous high balls and hors d'oeuvres. He felt nauseated and went home about 2 a.m. He recalls no dysphagia. He vomited once. He still felt nauseated and retched; finally, he induced vomiting again by putting his finger down his throat. About this time he felt agonizing substernal pain. The pain became unbearable and he was seen by Dr. Apfel at 7 a.m. He was given a hypodermic injection of one quarter grain of morphine sulfate, which was followed by three similar injections during the course of the day with little relief of the pain. Oxygen by mask also did not help. Two electrocardiograms during the day were negative. When I saw him on the night of January 1, 1945, the substernal pain was so severe that he thrashed around the bed and it was difficult to question him. Physical examination was negative apart from a pulse rate of 100 per minute. There was no obvious difficulty in breathing. The temperature and blood pressure were normal.

With such intense substernal pain of sudden onset, the first diagnosis considered had been myocardial infarction. However, the two negative electrocardiograms spoke against this diagnosis. And in myocardial infarction the patient hardly ever thrashes around. Because of the history that a lesion of the esophagus had been detected (details were not known at the time), the possibility of a tear of the esophagus induced by violent retching and vomiting was considered. The substernal pain continued; it was only partially alleviated by morphine.

The patient was admitted to the Mount Sinai Hospital on January 5, 1945. He complained of burning substernal pain. X-ray studies by Dr. Sussman were reported as showing "no evidence of air in the mediastinum. Barium shows an obstruction in the

lower end of the esophagus corresponding to the site where in 1941 a smooth filling defect was noted. The defect at the present time is very much larger than that seen in 1941. The esophagus above this is slightly dilated. In some films the possibility is suggested that in addition to the tumor mass there is impacted food. On others, however, the impression is more that of a tumor mass which is greatly increased in size since 1941 and is producing obstruction."

On January 6, 1945, esophagoscopy was performed by Dr. Kramer who reported that "at 34 cm. from the upper incisor teeth the mucosa is swollen and reddened, mainly anteriorly, with approximation of the anterior and posterior walls. Advise waiting for about one week if course is satisfactory and then reexamining the esophagus."

Substernal pain persisted. There was profuse salivation and frequent regurgitation of the liquids which were all he was given. The temperature was most often under 100°F. On January 12, he had a chill and the temperature rose to 102.8°F., but quickly fell; on January 17, the temperature again rose to 103°F. but dropped soon to 100°F.

On January 17, esophagoscopy was repeated by Dr. Kramer and his report read as follows: "Marked esophagitis, worse as lower esophagus is approached. There is thick exudate and old blood in large quantities. At 36 cm., yellowish, lobulated growth on left wall. *On posterior wall just below this level (37 cm.), there is a transverse tear of the posterior wall; old brownish blood coming from here. Esophagoscope passed below to cardia and Levin tube passed.*"

Esophagoscopy done by Dr. Kramer on January 19 revealed: "Practically no fluid in esophagus. Esophagitis (exudate and swelling of mucosa) practically gone. Tear of esophageal wall not visualized. Levin tube inserted."

On January 20, the patient, as a result of cough, brought up the Levin tube. Examination revealed edema of the right pyriform sinus and arytenoid. Esophagoscopy by Dr. Kramer revealed: "No tear seen. Tube not put back because of edema."

The patient continued to have substernal pain; he regurgitated liquids and salivated profusely.

X-ray examination on January 20 and 21 was found to disclose an "appearance most suggestive of an extra-esophageal collection of fluid and air which is sharply loculated.

Exploration of the mediastinum by Dr. Harold Neuhof showed enormous dilatation of the lower esophagus but disclosed no evidence of any extraesophageal lesion. Jejunostomy was performed by Dr. Ralph Colp.

After this the patient improved rapidly and the tube was removed. He was discharged from the hospital on February 13, 1945, feeling well and has continued in excellent health since. There has been no dysphagia on a normal diet. The only restriction has been abstinence from alcohol.

*Case 2.* A man of forty was seen in January, 1937, at Parsons Hospital. After a protracted drinking bout lasting several days, during which he vomited repeatedly, he was seized with violent pain poorly localized in the upper abdomen and lower anterior chest. Exploratory laparotomy by Dr. Robert Yanover proved negative. The pain then became localized in the substernal region and the patient seemed to be going into shock. Myocardial infarction was considered. However, subcutaneous emphysema then appeared in the neck and later the chest; rupture of the esophagus was then the obvious diagnosis. The patient was then seen by Dr. Arthur Touroff to consider the advisability of mediastinotomy. However, his condition had become so rapidly aggravated that such intervention did not seem feasible; an incision was made into the subcutaneous emphysema as the root of the neck. The patient sank rapidly.

Necropsy was performed by Dr. Samuel Barland: "The postier surface of the esophagus was found lying in a bed of brownish, necrotic material. The necrotic material extended into the upper part of the mediastinum. On tying off the esophagus and duodenum, slight pressure on the stomach caused gastric juice and air to bubble through the esophagus just above the junction with the stomach. Section of the esophagus showed a laceration one inch long, covered by clotted blood, just above the cardiac portion of the stomach. A



probe could easily be passed through this lacerated area into the mediastinum. A second laceration parallel to the first and one-half inch long, is also present. No probe can be passed through this second laceration. Sections through these lacerations show hemorrhagic material in the adjacent and underlying tissue. Search of the mediastinum and esophagus for foreign body met with no success."

#### DISCUSSION

Two cases are described in which laceration of the esophagus produced violent substernal pain simulating that of myocardial infarction. In both patients, however, the diagnosis of esophageal tear was established during life. In one case rupture of the esophagus was indicated by the appearance of subcutaneous emphysema; in the other the history of old esophageal disease led to esophagoscopy and visualization of a tear of the inner coats of the esophagus.

In both patients the tear of the esophagus was due to violent vomiting induced by alcohol. That forceful vomiting very rarely ruptures a normal esophagus has long been known (see Gott (2) for the literature, which dates back to Boerhaave). The laceration is doubtlessly produced through the intermediacy of increased intraesophageal pressure. The reason why vomiting so rarely results in rupture of the gullet is indicated by the old finding of MacKenzie (3) that from five to eleven pounds of water pressure within the esophagus are required to rupture the organ. The chief clinical conditions in which vomiting sufficiently violent to rupture the esophagus may occur are alcoholism and intracranial lesions.

In the second patient the post mortem examination revealed no evidence of previous esophageal disease, so that the case is to be regarded as one of the rare instances of spontaneous rupture of a previously normal esophagus due to vomiting. In the first case there was an antecedent esophageal lesion, presumably a benign tumor, which probably weakened the esophageal wall so as to predispose to rupture by increased intraesophageal pressure.

The findings during mediastinotomy in the first patient demonstrated that the laceration involved only the inner coats of the esophagus so that there was no complete perforation and no mediastinitis. The writer is not acquainted with similar observations, i.e., laceration of the inner coats of the esophagus demonstrated by esophagoscopy and absence of complete perforation with mediastinitis proved by mediastinotomy. It is of interest that the esophagoscopy showed that the laceration was accompanied by esophagitis. It is likely that the use of penicillin prevented outward extension of infection from the laceration and esophagitis; such outward extension of infection with resultant mediastinitis and a generally, though not invariably, fatal outcome seems to have been the usual course of events in the past. With penicillin available, the prognosis of perforation of the esophagus should be less gloomy than hitherto.

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## A SECOND CASE OF IRREDUCIBLE PROLAPSE OF THE UTERUS

ROBERT T. FRANK, M.D.

(*New York, N. Y.*)

In 1938 I presented a patient who suffered from an irreducible prolapse of the uterus, complicated by strangulation, sliding hernia of the cecum and intestinal obstruction (1). At that time I emphasized the rarity of irreducible prolapse and the scantiness of the literature pertaining to this complication.

Recently I have encountered another case of irreducible uterine prolapse due to different causes and showing different complications.

### CASE REPORT

On January 4th, 1946, Mrs. L. K., aged fifty-six, presented herself at my office. She proved to be a thin, short, little wisp of a woman who could barely stand and who fainted several times in the course of the next hour. According to the history which I elicited from the patient and her grown daughter, the menarche developed at 14 years. Regular menstruation ceased some 7 years ago (at the age of 49 years) since which time the patient has bled almost daily in varying amounts. For 2 years there has been an increasing protrusion from the vulva. The prolapse became completely irreducible one year ago. Some 9 months ago the patient entered a hospital, received two blood transfusions but left, against advice, when operation was suggested.

Because of the weak general condition, examination at this time was cursory. The patient was emaciated (weight 77 pounds). There were blowing systolic and diastolic murmurs over the cardiac area. A globular mass was felt above the symphysis, noticeably bulging out the otherwise scaphoid abdomen.

A large complete prolapse, with eversion of the anterior and posterior vaginal walls, protruded between the thighs. The surface of the everted vagina was dry and scaly, the portio flat, large, eroded. A small amount of pale blood appeared at the external os.

On the Tallquist scale, the hemoglobin proved lower than 20 per cent. Because of the desperate physical condition, I coerced the then slightly paranoid and recalcitrant woman to enter the Gynecological Ward of the Mount Sinai Hospital. Although I had become consultant in 1937 and therefore no longer functioned on the ward service, Drs. Rubin and Goldberger invited me to treat and to operate upon this patient. I may say that without the exceptional skill, care and devotion which was lavished on this woman by the resident staff and nurses, she never would have weathered the severe complications which developed.

On admission the hemoglobin was found to be 11 per cent! The red cells showed achromia, microcytosis and anocytosis. The urine contained 5-7 rbc per HPF. The urea nitrogen was 9 per cent, the urinary concentration never rose above 1012. The P.S.P. test showed less than 10 per cent excretion of the dye. I.V.P. showed bilateral hydronephrosis. The excretion was too poor to visualize the lower portion of the ureters which entered the prolapsus.

By means of 4 transfusions the hemoglobin was raised from 11 to 53 per cent.

Operation was performed on January 17th, 1946. The occasion was elevated into a real family reunion, my assistants being Drs. I. C. Rubin, Morris A. Goldberger, Emanuel Klempner, and Jack Squire. Never before have I performed an operation with such a distinguished galaxy of assistants.

The abdomen was opened by a left paramedian suprapubic incision. This exposed a solid tumor, 17 x 10 x 8 cm., which fitted snugly upon the pelvic brim and partly filled the true pelvis. Traction raised the mass sufficiently to disclose a thick pedicle which entered and disappeared within the extra-abdominal prolapse. By combined traction above and

pressure upon the prolapse from below, inversion was accomplished. The enlarged uterus and the bladder now rose into the abdomen. The right cystic adnexae were firmly adherent to the right side of the uterus. A typical high supravaginal hysterectomy and bilateral salpingo-oophorectomy was now performed. The abdomen was closed in layers. During the operation, 1000 cc. of blood was given intravenously (fig. 1).

The pathological report stated that the tumor consisted of a combination of theca cell and granulosa cell tumor. The uterine endometrium was hyperplastic, and uterine fibroids and adenomyosis studded the myometrium.

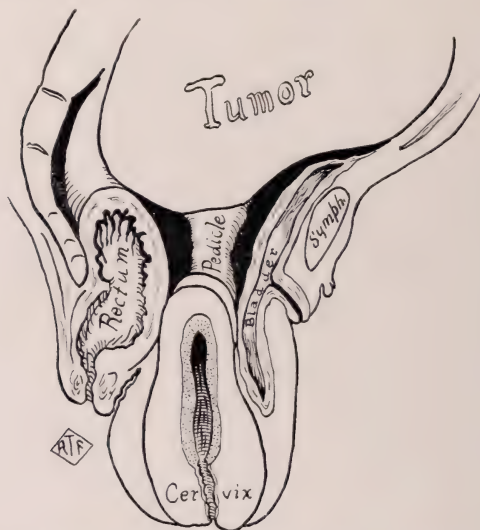


FIG. 1. Schematic sagittal section through pelvis and prolapse

The tumor is fixed upon the pelvic brim, its lower pole filling the true pelvic cavity. A thick, short pedicle arose from the left cornual region. The uterus was enlarged with hyperplastic mucosa.

The postoperative course was stormy. I condense the detailed account given me by Dr. Zakin, the resident gynecologist, who was in charge. The day after operation, pneumonia consolidation of the left lower lobe developed with temperature elevation to 103°F. Lysis occurred under combined sulfadiazine and penicillin therapy. On the 9th postoperative day, right lower quadrant and suprapubic pain developed, accompanied by nausea and faintness. 200 cc. of bloody urine were obtained by catheter. Temperature rose to 106 degrees, repeated chills developed. Urine culture showed staphylococcus aureus. No response to penicillin. Therefore, in spite of the poor kidney function, sulfadiazine was given intravenously. Blood culture showed gram positive cocci. Patchy consolidation appeared in both lungs. The patient's condition became critical—clouded sensorium, fecal incontinence, cyanosis, abdominal tenderness and distension. The patient was transfused, put in an oxygen tent, and given large doses of adrenal cortical extract. Two

days later marked improvement developed although the lung signs and the bloody urine persisted. The improvement continued. P.S.P. excretion rose to 30 per cent. The patient signed out against advice when able to walk on the 21st day after operation.

On returning home the prolapse recurred but could be reduced readily. I attempted, in vain, to keep the prolapse up by means of Gellhorn, Schatz and other pessaries.

The patient was readmitted to the gynecological service on March 8th. During her stay at home she had undergone another attack of pyelonephritis—high fever, bloody urine. Urine culture showed *b. pyocyaneus*.

On March 21st, I performed a typical Manchester operation on the much involuted genital tract. The sole divergence from my usual technic (2) was necessitated by the shortness of the cervical stump. It was excised and the two parametria united in the median line. A high perineorrhaphy completed the procedure. Convalescence was smooth; discharged April 15th, 25 days after operation.

On June 12, 1946, about six months after removal of the tumor and three months after the vaginal plastic operation, I reexamined the patient. She looks well, her demeanor is normal. Her weight has risen to 91 pounds; the hemoglobin is 88 per cent. The abdominal scar is firm, the perineum high as is the vault; some relaxation of anterior vaginal wall. Stilbestrol was prescribed for the flushes.

#### COMMENT

The clinical picture of this case is complex. After the menopause, reactivation of the bleeding function developed in consequence of the hormonal action of a theca-granulosa cell tumor. Persistent bleeding continued unchecked for seven years. The patient's hemoglobin eventually fell to 11 per cent. A potential prolapse became overt as the uterus increased in size and weight, and as pressure from above was exerted more and more by a growing left ovarian tumor. At a certain time and point the eversion became irreducible. Following hysterectomy and double oophorectomy, and consequent withdrawal of the estrogenic-progestational stimuli, a tremendous involution of cervix and vagina followed, which made the performance of the final plastic operation far simpler. At first it had appeared necessary to perform a Le Fort operation or a complete colpectomy.

In the light of my experience with these two cases of irreducible prolapse, I can state unequivocally that operative intervention should be by means of the abdominal approach, never *per vaginam*, because by the vaginal route the technical difficulties will prove insurmountable.

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## THE REPAIR OF INTRACTABLE RECTOVAGINAL FISTULA: A NEW PROCEDURE

JOHN H. GARLOCK, M.D.

(New York, N. Y.)

In a volume commemorating the scientific accomplishments of Dr. I. C. Rubin, it would seem *apropos* to confine one's contribution to some subject closely allied to the general field of gynecology. I would like, therefore, to discuss observations on the operative repair of rectovaginal fistula and report an operative procedure which can be utilized in the correction of such fistulae which have resisted the usually accepted methods.

The gastro-intestinal surgeon is as frequently confronted with the problem of rectovaginal fistula as is the gynecologist and, on the basis of a fairly large experience with this anatomical complication, it has become apparent that there may be many underlying causes. In order of frequency, these may be enumerated:

1. *Fistula due to injury.* The injury may be of two varieties. In the first, a third degree tear of the perineum may occur during childbirth and, during the subsequent repair, an incomplete or poorly executed operation may result in the formation of a fistula between rectum and vagina. Usually, these openings are located at or near the sphincter ani muscles. In the second variety, the injury occurs during the performance of a perineorrhaphy for the correction of rectocele. One of the sutures used to approximate the levator ani muscles may inadvertently include part of the anterior rectal wall with subsequent local necrosis and fistula formation. These are usually located at a higher level. I have seen an appreciable number of patients falling into these categories.

2. *Fistula secondary to non-specific ulcerative proctitis.* In our work with ulcerative colitis, there has been noted a fairly large incidence of associated rectovaginal fistula. The underlying pathological basis for the development of such fistulae is, of course, the extensive ulcerative disease in the rectum with spontaneous perforation through the thin rectovaginal septum.

3. *Fistula secondary to carcinoma of the rectum, vaginal wall or uterine cervix.* This is a late manifestation of the primary disease.

4. *Fistula resulting from luetic or tuberculous disease of the vaginal wall or as a complication of lymphogranuloma inguinale.*

5. *Fistula following intensive radiation therapy for carcinoma of the cervix uteri.* These fistulae are usually very large and may involve destruction of most of the rectovaginal septum. Recently, a case of this type came under observation in the Mount Sinai Hospital.

The diagnosis of rectovaginal fistula should offer no difficulty. The story of the spontaneous escape of gas and feces from the vagina is sufficient to indicate its presence. Careful vaginal and rectal examination will demonstrate the location, size and course of the fistulous tract. It seems superfluous to emphasize the need for a careful history into the antecedent factors concerned with the



development of the opening. Finally, the examination should always include a speculum visualization of the whole vagina and cervix and, what is most important, a thorough sigmoidoscopic observation of the rectal and sigmoidal mucosa. The disclosure of the presence of an underlying ulcerative proctitis, for instance, will alter the entire plan of surgical therapy. In the same way, the finding of a carcinoma of the rectum will call for an operation more radical in nature.

We are not concerned here, primarily, with rectovaginal fistulae secondary to carcinoma, ulcerative colitis, tuberculosis or lymphogranuloma. The approach to the problem in these diseases is quite different and is concerned mainly with the treatment of the primary cause. For instance, in fistula secondary to ulcerative colitis, it is useless to attempt operative repair of the opening in the presence of an underlying diseased rectum. Each operative attempt is doomed to failure because the marked inflammatory infiltration of all the rectal and perirectal tissues will prevent satisfactory healing of the repaired structures. A few years ago, there came under observation a patient who had had nine operations for the repair of a fistula secondary to ulcerative colitis. Naturally, the fistula reformed very quickly after each procedure. A complete appreciation of the underlying disease would have prevented these useless operations.

Our discussion in this article is concerned mainly with rectovaginal fistula secondary to obstetrical or operative injury. There is no question about the fact that the vast majority can be satisfactorily repaired by a fairly simple operation. This consists of the raising of a vaginal flap after incising the posterior fourchette transversely, circumcising the fistulous opening, repair of the hole in the rectum, following extensive lateral mobilization of the rectal wall from the vagina, and the approximation of both levator ani muscles in the midline as is done in the performance of a perineorrhaphy for relaxed perineum. Occasionally, however, one is faced with the problem of a twice or thrice recurrent fistula with the production of extensive scarring in the perineum and rectovaginal septum which will not respond to operative methods heretofore described. It was for this type of case that the operation to be described was devised. It is founded on the basic surgical principles of thorough pre-operative preparation and the replacement of scarred tissues by normal tissues of excellent vascularity.

The history of this patient is most unusual not only from the standpoint of the recurring rectovaginal fistula, but also because of the many other operations which she endured for unassociated diseases. The rapid and uncomplicated recovery after each major operation is a tribute to the fortitude and recuperative powers of the human organism.

*History.* Mrs. M. K. was 36 years of age when she first came under observation in October of 1939 for a moderately severe exophthalmic goiter of approximately six months' duration. The basal metabolic rate was plus 30 per cent and there were evident all the signs and symptoms of hyperthyroidism, including moist skin, fine tremor of the hands, mild exophthalmos and a pulse rate ranging between 100 and 116. She was admitted to the hospital, where, after twelve days' preparation, I performed a subtotal thyroidectomy. Convalescence was uneventful and she was discharged on the sixth postoperative day.

In May of 1940, she came in to see me and told the following story. Five and one-half years ago she had her first baby. During the delivery, which was difficult, it was necessary to perform an episiotomy in order to prevent an extensive perineal tear. The wound was repaired by the obstetrician immediately following the birth of the child. Exactly seven days later she noted the escape of gas and feces from the vagina and it became evident that there was present a rectovaginal fistula. At that time she was advised to have the fistula repaired, but she decided, instead, to have her second child first. As it turned out, hers was a wise decision. One year later the second child was born without any difficulty.

In the following year, the first attempt at repair of the fistula was carried out by one of New York's prominent gynecologists. The fistula recurred seven days postoperative. The same surgeon attempted a second repair a year later and the fistula recurred in five days. Following the second repair, the patient noted some diminution of rectal control. In November of 1939, one month after the thyroidectomy, the third operation for repair of the fistula was carried out by another gynecologist. The fistula recurred in three days. However, following this procedure, rectal control was considerably improved. In discussing the details of the preparation for each of these operations, it was disclosed that each time the patient was operated upon the day after admission to the hospital and that the preparation consisted of a cleansing douche and enema.

*Examination.* The patient was nervous and distraught. She mentioned suicide if repair of the fistula could not be consummated. Locally, the findings were as follows: The perineum was relaxed and the levator ani muscles were widely separated. The anterior half of the posterior vaginal wall was scarred and firm. Just within the vaginal introitus in the midline was seen a fistulous opening measuring  $\frac{3}{4}$  of an inch in diameter. A probe was inserted and entered the rectum at a point between the external and internal sphincter and muscles. At and surrounding the fistula, the rectovaginal septum was thin. The tone of the sphincter ani muscles seemed good and there was fair active contractility. Speculum examination of the vagina revealed no other abnormality. The remainder of the pelvic examination was negative. Sigmoidoscopy showed normal rectal mucosa.

Operation was advised, but the patient decided to defer it until the following winter.

She was finally admitted on January 6, 1941. Examination at that time showed no essential change in the local condition since the first observation. Realizing that adequate preoperative preparation constituted an important part of the therapy, the following regime was instituted: 1) A low-residue constipating diet, 2) Prolonged cleansing vaginal douches twice daily, 3) Daily colonic irrigation, 4) The administration of sulfanilamid gm. 1 every four hours. At that time, we were engaged in a study of the effect of the parenteral use of the sulfonamids in colon surgery.

It was thoroughly demonstrated at that time, and since then repeatedly confirmed, that the parenteral administration of these drugs was much more effective than its local use in the prevention of infection. At the present time, I would use one of the insoluble sulfonamids, such as sulfa suxidine or sulfa quanidine in order to diminish the bulk of the fecal content. 5) Small doses of deodorized tincture of opium. This preparation was carried out over a period of four full days.

*Operation.* (January 10, 1941.) The operation was carried out under nitrous-oxide and ethylene gas anesthesia. The fistula was located between the external and internal sphincter muscles (fig. 1). A transverse incision was made in the posterior fourchette and a flap of vaginal mucosa was dissected upward, separating the vagina from the fistula. The vagina was dissected away from the rectum upward and laterally. The opening in the rectum was closed with interrupted sutures of fine chronic catgut (fig. 2). These sutures were placed so as to have the knots face toward the rectum. In order to obviate using the scarred avascular tissues immediately available, it was decided to interpose between rectum and vagina at the site of the fistula a cushion of vascular muscle in a manner similar to the operation I described in 1928 for vesicovaginal fistula. Accordingly each levator ani muscle was mobilized and a pedicled muscle flap was fashioned from each anterior edge with the pedicle located inferiorly (fig. 3). The right flap was placed across the repaired rectal opening and sewn into place with interrupted sutures of fine silk. The opposite flap was

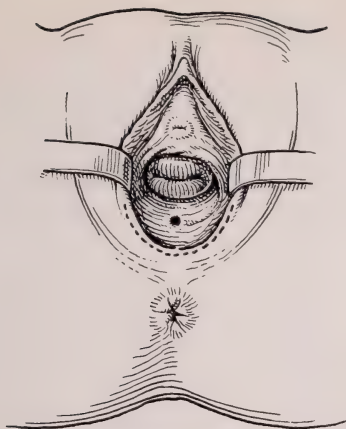


FIG. 1. Sketch of the condition at the time of operation, with the fistula indicated and the incision in the fourchette.

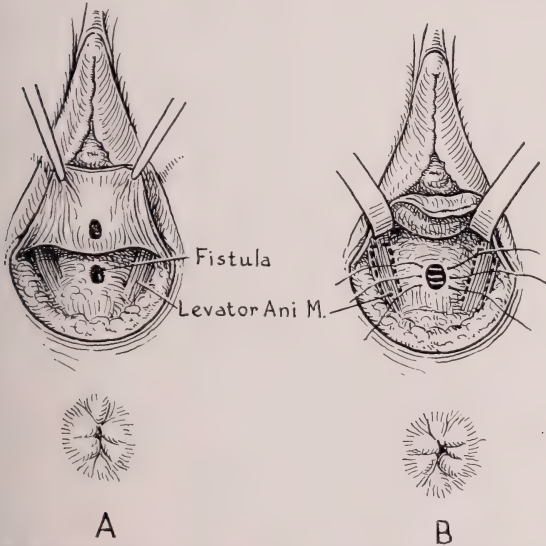


FIG. 2a. Vaginal flap has been lifted and the rectum mobilized well laterally on each side bringing into view the levator ani muscles.

2b. The opening in the rectum is being repaired with interrupted sutures. The outline of the pedicled muscle flaps along the anterior edge of the levator ani muscles is indicated.

then placed on top of its fellow and held in place by the same method. Bleeding was then fully controlled and the vaginal mucosa was closed in a vertical direction with fine chromic stitches. The vagina was packed with gauze and an indwelling catheter was placed in the bladder.

*Course.* Convalescence following this operation was relatively uneventful. The vaginal packing was removed on the fifth day. The bladder catheter was maintained for one week. The bowels were constipated for nine days by the use of a liquid diet and tincture of opium. The patient passed gas without difficulty after the second day. A rectal irrigation was given on the tenth day without untoward effect on the repaired fistula. On the eleventh

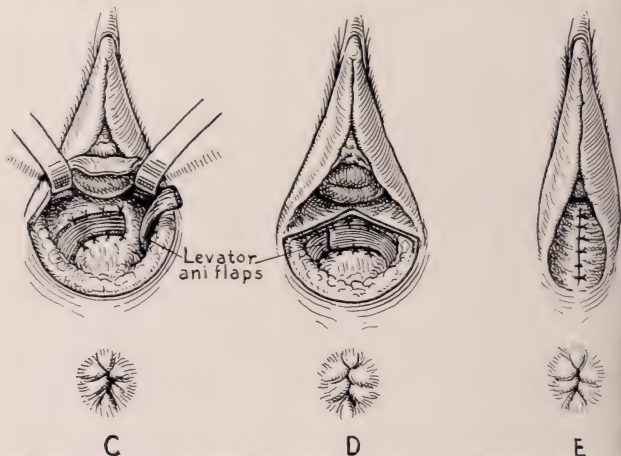


FIG. 3c. The right muscle flap has been placed over the repaired fistula in the rectum and is being sewn to the wall with interrupted silk sutures.

3d. The left muscle flap is superimposed on the one of the opposite side and sewn in place in a like manner.

3e. The finished operation following repair of the vaginal incision.

day, the patient complained of throbbing pain in the perineum. This was found to be due to the presence of a small hematoma which was evacuated. The perineal wound healed by first intention. The patient was discharged on the fourteenth postoperative day with complete healing of the operative wound and with normal rectal control. Since then she has had no symptoms referable to this region.

During the discussion of this patient's past history, I forgot to mention that prior to her marriage she had had three operations; tonsillectomy, appendectomy and oophorectomy for large ovarian cyst.

The subsequent surgical history of this patient is interesting from many standpoints. In October of 1941, she began to complain of symptoms suggestive of peptic ulcer. A gastrointestinal x-ray examination on October 23, 1941 disclosed an irregularity in the pyloric antrum with mucosal hyperplasia which suggested the presence of an ulcer. A repeat examination one month later showed an ulcer defect one-half inch in diameter and one inch proximal to the pylorus. Gastroscopy suggested a benign basis for this ulcer. Medical therapy was instituted and after four weeks repeat gastroscopy indicated complete healing.

Gastric analysis, however, showed an almost complete anacidity. Because of this finding, the gastro enterologist advised operation. During the succeeding ten months the patient had almost constant pain radiating through to the back and she lost twenty pounds in weight. Another x-ray examination in September of 1942 showed fixation of the rugae of the stomach in the region of the ulcer, which suggested very strongly the possibility of carcinoma. Operation was urged and accepted.

On October 22, 1942 I performed a partial gastrectomy for a large penetrating ulcer of the stomach. The ulcer, one inch in diameter, was located in the pars media of the stomach and had perforated into the pancreas. Thorough microscopic examination failed to reveal any evidence of neoplasm. Convalescence was uneventful and she was discharged on the fourteenth day.

A few months later she had a radical operation done for chronic severe sinusitis involving the ethmoid and sphenoid sinuses. This corrected a long-standing cause for repeated infections.

On November 5, 1943, the patient returned again complaining of pain in the rectum and right lower quadrant. There were no menstrual irregularities. Examination showed the presence of a large uterine fibroid projecting from the posterior surface of the uterus toward the sacrum. It could be lifted out of the pelvis with difficulty. In addition, there was felt a cystic mass in the right fornix about three inches in diameter which was taken to represent an ovarian cyst.

Operation was carried out on November 30, 1943 and consisted of supra cervical hysterectomy and resection of the right ovary for a dermoid cyst. The left ovary had been removed many years before. A small amount of functioning ovarian tissue was left following removal of the cyst. Convalescence was smooth and the patient was discharged on the tenth day. She has remained well since then.

#### SUMMARY

There is reported herewith a new operative procedure for the repair of intractable rectovaginal fistula. Emphasis is placed on the importance of thorough preoperative preparation. The gastro-intestinal surgeon has long been mindful of the need for this complete preparation of a patient about to undergo an intestinal operation. The details of the operation take into account a basic fundamental principle of general and plastic surgery. In essence, this means that, when attempting repair of anatomical structures, one should discard rigid poorly vascularized scar tissue and substitute for it normal soft material of great vascularity. Normal muscle tissue in the form of pedicled flaps meets these requirements. Finally emphasis should be placed on the need for an atraumatic surgical technique with fine instruments and fine suture material if optimum results are to be obtained.

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## HYPOPHYSIO-HYPOTHALAMIC INTERFUNCTIONS AND DYSFUNCTIONS<sup>1</sup>

JOSEPH H. GLOBUS, M.D., ALVIN I. GOLDFARB, M.D. AND  
SOLOMON SILVER, M.D.

### SECTION I

#### *Introduction*

The pituitary, frequently called the "master gland of the body" or "central ganglion" of the endocrine system with good reason, is prominent in maintaining the internal economy of the organism because of its significant influence in regulating visceral activities. This function of the pituitary depends in large part on its intimate relationship with the hypothalamic division of the central nervous system. Thus, in discussing the pituitary, its functions and dysfunctions, it is necessary to consider the hypothalamus thoroughly.

In recent years clinical studies and laboratory tests on human material have increased our understanding of the role of both the pituitary and the hypothalamus in the maintenance of balanced functions of the organism. However, the relatively infrequent occurrence of frank pituitary or hypothalamic disorders in man, together with the difficulties met in the study of such disorders, are still blocking clarification of the part played by these two structures in health and disease. Some of these difficulties were overcome by the discovery that experimental studies when compared with clinical data indicate the existence of great similarities of reaction of man and animal to disturbed pituitary and hypothalamic functions. Most of the available information on the functions and dysfunctions of this gland and the related structures is derived from observations made, for the most part, on experimental animals. Moreover, in the case of the pituitary gland, in recent years by isolating and purifying many of the hormonal products of the pituitary and other glands of internal secretion biochemists have opened the way toward a better understanding of the inter-relationship of the several endocrine glands, their interdependence, and their effect on metabolism and other visceral functions. This in turn resulted in a substantial contribution to the present-day knowledge of the balancing interactions of the central and vegetative (visceral) nervous systems.

The anatomical relationship between the hypothalamus—the seat of regulatory centers of the vegetative nervous system—and the pituitary is intimate, and their significant physiological interdependence is revealed by a study of manifestations of expanding lesions of either structure. A tumor of the pituitary by disrupting or otherwise disturbing the hypothalamus is found to provoke a disorder of the nervous system; conversely an expanding lesion of the hypothalamus, the infundibulum, or the tuber cinereum by secondarily implicating

<sup>1</sup> Read by the senior author as part of the symposium on Visceral Insufficiency at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on April 17, 1946.

From the Neuropathology Laboratory, The Mount Sinai Hospital, New York.

the pituitary often results in disturbances usually assigned to pituitary disease.

No less significant is the fact that because of the intimate anatomical relationship between the hypothalamus and the pituitary, a disease almost totally restricted to the hypothalamus may produce symptoms and signs of so-called pituitary dysfunction. This is not only true of lesions limited to the hypothalamus but also occurs when neighboring or more remotely located lesions produce effects which cause changes in the hypothalamic nuclei. One of us (J. H. G.) has reported a series of cases in which increase of pressure within the third ventricle due to obstruction of the Sylvian aqueduct caused disruption of the hypothalamic floor associated with signs of hypothalamic dysfunction such as obesity, amenorrhea and sexual dystrophy. Such signs of hypothalamic disturbances in the past often were erroneously attributed to primary pituitary dysfunction. This error probably occurred because, as has already been indicated, there is an apparent overlapping of hypothalamic and pituitary functions in which the hypothalamus either alone, or by acting upon the pituitary, produces endocrine changes.

With the foregoing in mind, an attempt is made in this review to take inventory of concepts adequately supported by experimental and clinical observations with emphasis on those which have contributed to the further understanding of pituitary dysfunctions and have merited general acceptance. This is followed by an account of the accumulated information on the significant clinical, physiological and pathological factors operative in the several constellations of signs and symptoms (syndromes) expressive of pituitary and hypothalamic disorder.

Because lucidity and brevity in this presentation is our aim, it became necessary to make a careful selection of material with the omission of that which, though of interest, was likely to obscure rather than illuminate the points in question.

### *The hypophysis: its embryology and anatomy*

The pituitary consists of several well defined component parts. This is in accord with the fact that in its embryogenesis there are two independent primordia, or sources of origin: an evagination of the roof of the buccal cavity, and a protrusion of the floor of the third ventricle in the regions which later form the tuber cinereum (fig. 1). The two fuse with one another in the course of their development to form the hypophysis; they retain a certain anatomical independence and form the two main subdivisions, the anterior and posterior lobes of the gland (fig. 2).

The *anterior lobe* of the hypophysis is its glandular portion and is almost entirely derived from an outpouching of the ectodermal lining of the roof of the oral cavity. The *posterior lobe*, or *pars posterior*, is formed from an outpouching of neuroectodermal tissue of the floor of the diencephalic (third) ventricle. The projection from the floor of the third ventricle assumes a position somewhat posterior to the outpouching of the oral ectoderm. Progressive growth of the oral evagination converts it into a pouch (Rathke's pouch) which first maintains connection with the roof of the oral cavity by means of a solid

cord of cells and then undergoes a rotation resulting in discontinuation of its attachment to the roof of the oral cavity. It then envelops the neuroectodermal prolongation, both anteriorly and laterally, and may deposit some relatively primitive cells on the anterior and dorsal aspects of the hypophyseal stalk. The original ectodermal pouch (Rathke's pouch) forms a cleft, the

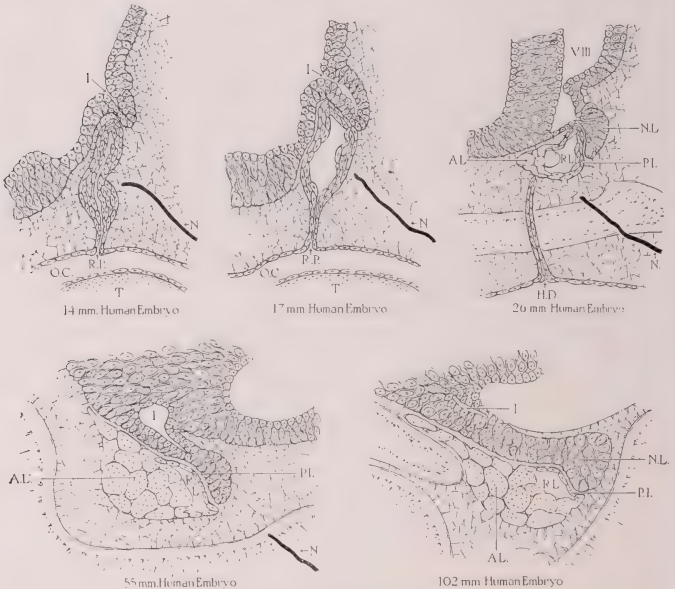


FIG. 1. Semidiagrammatic drawing illustrating the several stages in the development of the pituitary body. R.P. (Rathke's pouch); O.C. (Oral cavity); I. (Infundibulum); N. (Notochord); T. (Tongue); H.D. (Hypophyseal duct); A.L. (Anterior lobe of the hypophysis); R.L. (Residual lumen of Rathke's pouch); P.I. (Pars intermedia of the hypophysis); N.L. (Neural lobe of pituitary); and V. III (Third ventricle). (Modified, from Atwell.)

lining cells of which comprise the pars intermedia (or pars infundibularis) of the fully developed gland. Thus, in its development the glandular portion of the hypophysis gives rise to three parts: the pars tuberalis, pars infundibularis and pars distalis. The pars tuberalis is a rather thin layer of tissue adherent to the tuber cinereum. The pars infundibularis is that part of the glandular lobe which surrounds the infundibular stem of the pars nervosa, and is continuous on one hand with the pars tuberalis, dorsally, and the pars distalis, ventrally. The latter comprises the major part of the glandular (anterior) lobe.

*Secretory cells of the anterior lobe of the hypophysis<sup>2</sup>*

The cellular elements of the pars distalis of the anterior lobe of the hypophysis are mainly of three types: chromophobe, eosinophile and basophile cells (fig. 3). In addition there are also recognized castration (signet ring) cells and pregnancy cells. The cells are usually classified according to the presence or absence of granules, and the affinity of these granules for certain acid or basic dyes. The

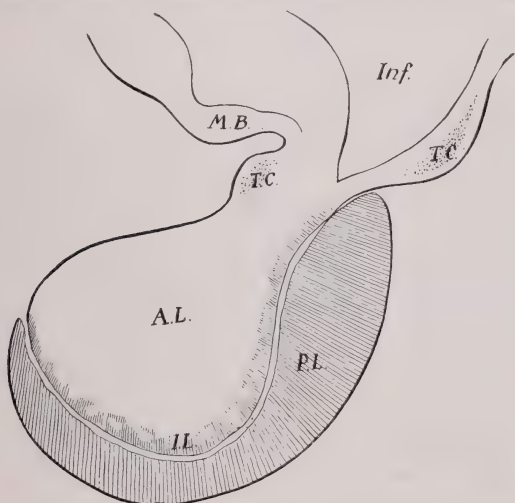


FIG. 2. Semidiagrammatic illustration of the several parts of the pituitary body and related structures: A.L. (Anterior lobe); P.L. (Posterior lobe); I.L. (Intermediate lobe); T.C. (Tuber cinereum); Inf. (Infundibulum); and M.B. (Mammillary bodies).

"acidophile" cells contain coarse, cytoplasmic granules of uniform size which stain brilliantly with acid dyes; the "basophile" cells contain less distinct granules which vary in size and are stained with basic dyes. The "chromophobe" cell is said to be devoid of "specific" granulation. The castration cells are modified basophile elements found after experimental castration, while the pregnancy cells are modified acidophile cells discovered during or after pregnancy.

Recently, however, it was demonstrated by Severinghaus that of all differences in the morphology of the cells, the Golgi apparatus may serve as the best means of identifying different cell forms. Thus, on studying the Golgi apparatus in cells of the anterior pituitary he reached the conclusion that the agranular

<sup>2</sup> Description of the histologic architecture of the glands is omitted because it does not contribute any significant data pertaining to the subject under discussion.

chromophobe cells are the parent cells from which the eosinophile (alpha) and the basophile (beta) cells develop.

There are wide individual variations in the differential counts of the cells of the glandular portion of the hypophysis. The average count is: chromophobes, 52 per cent; acidophile cells, 37 per cent; and basophile cells, 11 per cent. The ratio of cells may depart from the "normal average" with certain physiologic states of the organism; for example, in pregnancy, advanced age, and where removal of other glands of internal secretion or hormonal therapy has occurred.

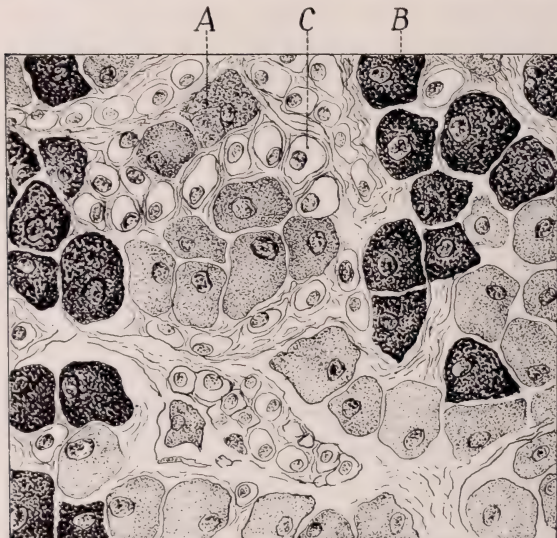


FIG. 3. Semidiagrammatic drawing of the component cells of the pituitary: A. (Eosinophiles); B. (Basophiles); and C. (Chromophobes).

It has been stated also that there is a relative increase in the basophile cells in hypertension and obesity, and it has been maintained that basophilia is associated with Cushing's syndrome; still other correlations have been suggested but thus far these matters have not been well substantiated.

#### *The posterior lobe of the hypophysis*

The posterior lobe of the hypophysis, or pars nervosa (infundibular process), is a solid bulb at the end of the infundibular stem, and is converted thereby into the infundibulum. It is partially enveloped by the glandular part of the pituitary (the anterior lobe). It consists of "neuroglial" tissue among which are scattered large branching cells called pituicytes and unmyelinated fibers from two



tracts (the supraoptic-hypophysial and tubero-hypophysial) connecting the hypothalamus and neurohypophysis. The only cell type of the posterior lobe to which a secretory activity can reasonably be ascribed are the pituicytes. These cells contain granules and undergo cyclic changes suggesting secretory activity.

### *Hormones of the hypophysis*

Numerous attempts have been made, on the basis of available clinical and experimental observations, to allocate responsibility for the elaboration of specific hormones (or their fractions) to the eosinophilic and basophilic granular cell-forms of the anterior hypophysis. The chromophobe cells, because of their lack of granules, are not considered to have a secretory function. How-

CHART I  
*Pituitary hormones*<sup>1</sup>

source	target organ <sup>2</sup>
<i>Anterior Lobe</i>	
Growth Hormone	Not defined
Gonadotrophic <sup>3</sup>	
Follicle Stimulating Hormone	{ Ovary (follicle) Testis (seminiferous tubules)
Luteinizing Hormone	{ Ovary (corpus luteum) Testis (interstitial cells)
Prolactin	{ Corpus luteum Mammæ
Thyrotrophic	Thyroid
Adrenocorticotrophic Hormone	Adrenal cortex
<i>Posterior Lobe</i>	
Alpha-hypophamine (pitocin)	Smooth muscle
Beta-hypophamine (pitressin)	Kidney tubules

<sup>1</sup> The list of hormones given in Chart I does not include hypothesized pituitary substances, the existence of which does not seem to be reasonably confirmed.

<sup>2</sup> The target organ is that tissue or organ on which the hypophyseal hormone exercises its maximum direct physiologically significant effect.

ever, the identification of either of the two granular cell-types with the production of specific hormones has not yet yielded convincing results. Recently, evidence was offered in support of the view that each granular cell type is capable of elaborating more than one hormone and that different hormones are elaborated during successive phases of the cellular secretory cycle. This hypothesis merits serious consideration because it explains how so large a number of hormones may be produced by so small a variety (only two) of cell types.

Hormones (or hormone fractions) have been extracted from the pituitaries of many animals (among them the ox, sheep, hog, and the whale). All of the hormones extracted are proteins. Those obtained from the anterior lobe of the hypophysis are grouped as *growth*, *thyrotropic*,<sup>3</sup> *lactogenic*, *adrenotropic*, and *gonadotropic* factors. From the posterior lobe, the *antidiuretic* hormone is obtained. All these hormones have been shown by experimental tests to be active in the normally functioning animal (chart I). Another pharmacolog-

<sup>3</sup> The spelling of "trophic" and "tropic" is used interchangeably throughout this paper without intention of conveying any difference in meaning.

ically active substance is obtainable from the posterior lobe but it is not certain whether it plays a part in normal physiology. This substance (alpha-hyphamine or pitocin) exerts pressor and oxytocic effects. A question still exists as to whether the antidiuretic hormone is a separate substance or only a part of a much larger protein molecule, a fraction of which produces the changes in blood pressure and smooth muscle tone. From the intermediate lobe of some animals a *melanophore expanding hormone* has been isolated; this hormone, if it exists in man at all, is probably of little significance.

Since the hormones listed in Chart I are capable of reproducing all of the known physiologic functions of the pituitary, it is reasonable to assume that pituitary dysfunction might manifest itself in constellations of symptoms and signs referable to either hypo- or hypersecretion of these hormones in a manner shown in Chart II.

CHART II

HYPOPITUITARISM	HYPERPITUITARISM
1. Inhibition or retardation of growth	Accentuation or augmentation of growth
2. Hypothyroidism	Hyperthyroidism
3. Hypogonadism	Hypergonadism
4. Hypoadrenocorticism	Hyperadrenocorticism
5. Diabetes insipidus	(Water retention; edema?)

### *The hypothalamus*

As already suggested, clinical manifestations apparently related to hypo- or hyperpituitarism may be provoked by lesions in the hypothalamic portion of the central nervous system. It is, therefore, also desirable to consider briefly the more important anatomical and physiological features of the hypothalamus and the results of its dysfunction.

An excellent definition of the hypothalamus is given by Foster Kennedy in his discussion of medical syndromes of the hypothalamus. He says, "The hypothalamus is the neuroglandular instrument in command of vital rhythm: the regularity of pulse, maintenance of body temperature, the balance of intake and output of fluid, the cycle of sleep, the integrity of body weight, periodicity of the menstrual rhythm—all these ebbs and flows seem to be instrumented through the area under consideration." Regulation of the aforementioned functions predicates the crucial location of the hypothalamus, as part of the diencephalon, in relation to other parts of the brain and in intimate connection with the pituitary.

*Anatomy.* The hypothalamus is comprised of the floor and part of the lateral walls of the third ventricle (fig. 4). An indentation of the surface of the third ventricle (the hypothalamic groove) demarcates its dorsal boundary; rostrally it abuts against the parolfactory and preoptic areas, the lamina terminalis and the anterior commissure. Its lateral boundaries are vaguely marked by the internal capsule and part of the subthalamus. Caudally its line of

separation from the midbrain is marked by the lower portion of the mammillo-thalamic tracts and the posterior perforated space.

The ventral portion of the hypothalamus constitutes the floor of the third ventricle; it overlies the optic chiasm, includes in itself the tuber cinereum, the infundibular process and stalk, the post-infundibular eminence, and the mammillary bodies (fig. 5). Accordingly the hypothalamus is usually divided into three portions: supra-optic, tuberal, and mammillary.

In general the hypothalamus is represented by a layer of gray (nuclear) matter, within which the nerve cells, special in type, form several groups (nuclei). The most significant and better defined of these groups are the following: the supra-optic, paraventricular, anterior hypothalamic; the ventro-medial tuberal; the arcuate, lateral, and posterior hypothalamic.



FIG. 4. Semidiagrammatic drawing illustrating the topography of the hypothalamus and the enclosed cell groups.

There are two important, well identified connecting tracts: the hypothalamo-hypophyseal and the tubero-hypophyseal. Both consist of nonmyelinated fibres. Fibres of the hypothalamo-hypophyseal tract arise in the supra-optic and paraventricular nuclei by one root, while another root springs from the arcuate and possibly other tuberal nuclei. The tract courses through the infundibular stalk and enters the posterior lobe of the pituitary (the neurohypophysis). The tubero-hypophyseal fibers according to Roussy and Moringer not only enter the posterior lobe but also provide innervation for the anterior part of the hypophysis.

The known afferent connections of the hypothalamus are chiefly with the olfactory centers. The most significant efferent tract is the dorsal longitudinal bundle of Schütz. It is composed of periventricular fibers (myelinated and nonmyelinated) which pass caudally through the midbrain just beneath the aqueduct. There it makes connections with the visceromotor nuclei. It is believed that it constitutes a part of the autonomic system.

Not without significance is the characteristic vascular pattern of the infundibular region of the hypothalamus. Globus and others have drawn attention to vessels entering the tuber cinereum and related parts, from the pial lining as large trunks, that branch out irregularly into smaller twigs. In their course they have a peculiar cork-screw outline and appear to be sinuses lined

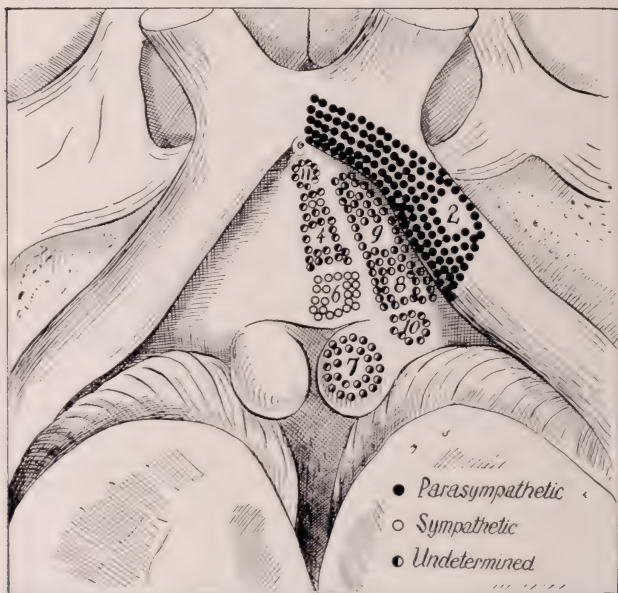


FIG. 5. Semidiagrammatic drawing illustrating the topography of the floor of the third ventricle and the enclosed nuclear masses.

by a single layer of endothelial cells which in turn is surrounded by a wide zone of a meshwork of fine glial fibers (fig. 6).

This peculiar vascularization of the infundibulum and tuber cinereum is best seen in the infant's brain until the fifth year of postnatal life, from then on it becomes progressively less apparent. There may be significance in the observation that in an instance of Cushing's syndrome the infundibular vessels and those of the tuber cinereum have retained the infantile pattern (fig. 7). This vascular pattern is a safe lead for the recognition of the infundibuloma, an autochthonous type of tumor, developing in and from the infundibulum.

*Physiology.* The importance of this part of the brain can be measured by

the facts, few as they still are, that have been established concerning its functions. The study of its development and its connections leads to the conclusion

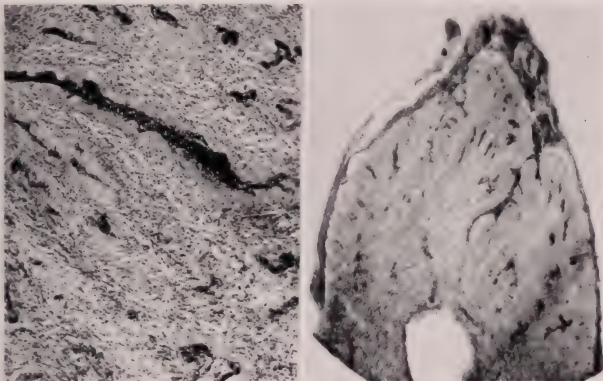


FIG. 6. Coronal sections of the infundibulum showing the typical porto-hypophysial vessels.

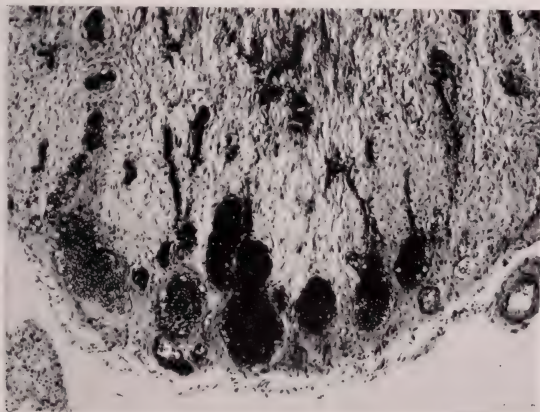


FIG. 7. Section of the infundibulum in a man, aged 49 years (case of Cushing's syndrome), displaying the vascular pattern characteristic of the infundibulum in the young.

that this part of the diencephalon is the seat of the supra-segmental control of the vegetative functions. Within this area are the central nuclei of the auto-



onomic nervous system (figs. 4, 5). As the central autonomic system regulator, the hypothalamus is in control of essential functions such as maintenance of water balance, temperature regulation, arterial tension, sleep and certain endocrine activities. Certain studies of the hypothalamic nuclei suggest some secretory activity for their component cells. In view of the scarcity of connecting tracts between the hypothalamus and the hypophysis, this observation demands serious consideration.

*Dysfunctions.* In the light of the known normal physiology of the hypothalamus and the functions allocated to its several nuclear groups, a number of clinical syndromes, resulting from localized hypothalamic lesions, may be postulated (Chart III). It is observed that lesions so situated may cause signs

CHART III

AREA OF HYPOTHALAMUS	EFFECT OF LESIONS	"SYNDROMES"
Anterior	Diuresis	Diabetes insipidus
Middle	Hyperglycemia	Froehlich's syndrome
	Gastric disturbances	Hyperthermia
	Gastric atonia	
	Mucosal hemorrhages	
	Disturb. of heat regulation	
	Obesity	
	Genital dystrophy	
Lateral	Cardiac acceleration	Fright and rage
	B. P. elevation	
	Dilatation of pupil	
	Inhibition of peristalsis	
Posterior	B. M. R. depression	Hypothermia
	Temperature depression	Hypersomnia
	Heart rate depression	
	Horner's syndrome	
	Lethargy	

similar to those caused by pituitary dysfunction. Signs of pituitary dysfunction in the presence of only hypothalamic disease indicate that it has a regulatory control over the hypophysis, augmenting or depressing its activity, and also that the hypothalamus may duplicate some of the hypophyseal functions. For these reasons some of the physiological disturbances associated with hypothalamic disorders have, in the past, been erroneously attributed to pituitary disease.

*Lesions in either the hypothalamus or the pituitary may result in pathologic obesity, sexual dystrophy, diuresis, and certain other vegetative dysfunctions.* In some instances of experimentally produced hypothalamic lesions (in rats) Smith observed skeletal dwarfism and infantilism in addition to obesity and genital atrophy.

As the central regulator of the autonomic nervous system, *the hypothalamus also exercises varying degrees of control over endocrine glands other than the hypophysis*

and by altering their function provokes signs of glandular dysfunction. So far as its regulation of the hypophysis is concerned, although there is some evidence for a direct nervous tract connection between the hypothalamus and the anterior lobe of the hypophysis, this has not yet been definitely established; hypothalamic control of anterior hypophysial secretory activity is probably mediated, at least in part, by way of the autonomic nerves which accompany vessels to the gland.

At this point it should be added that the hypothalamus, as a major integrating center, possesses some degree of "autonomy" but is influenced by—or better, as part of its integratory activity it is subject to—impulses from higher centers located chiefly in the frontal cortical areas of the cerebrum.

Hypothalamic dysfunctions liable to be misinterpreted as disorders of the pituitary may manifest themselves in constellations of signs and symptoms which, with some reservation, may conveniently be grouped as follows:<sup>4</sup>

Hypothyroidism	or Hyperthyroidism
Hypogonadism	or Hypergonadism
Hypoadrenocorticism	or Hyperadrenocorticism
Inhibition of growth; infantilism, dwarfism	or Acceleration of (selective) growth
Hyperphagia	

### *Obesity*

It is essential to distinguish between generalized obesity and the selective deposition of fat. In both conditions it is believed that the hypophysis exercises no direct effect on fat metabolism for neither destruction of the hypophysis, nor section of the infundibulum results in obesity. However, a disturbance in the elaboration and the balanced yield of the anterior hypophysial hormones acting upon, or through, the gonads may have a decided influence on the selective deposition of fat. A similar excessive selective deposition of fat (about pelvis and breasts) is encountered in lesions affecting the floor of the third ventricle. It is thus reasonable to assume that this type of dystrophy (selective deposition of fat) may be attributed to either an imbalance in pituitary secretions or to hypothalamic dysfunction. Hypothalamic lesions may produce such dystrophic obesity by altering some pituitary function or possibly by a direct influence on the gonads. The significance of the selective distribution of fat as an indication of an hypothalamic disorder was in fact first recognized by Erdheim. However, it was the classic case reported by Froehlich in 1901 which aroused great interest and initiated the many productive investigations of the causes of the syndrome now generally known by his name. Experimental and clinical studies have substantiated the hypothesis of Erdheim and the so-called "Froehlich's syndrome" is now considered to be chiefly due to a disorder of the hypothalamus.

Generalized obesity results when caloric intake exceeds the requirements of energy expenditure (fig. 8). In numerous controlled experiments it has been

<sup>4</sup> The importance of the hypothalamus in maintenance of proper water balance is to be considered when the posterior lobe of the hypophysis is discussed.

observed that obesity represents a surplus of ingested food and is not the direct result of any metabolic imbalance. There is ample clinical and experimental proof that hypothalamic lesions result in generalized obesity, and that the obesity

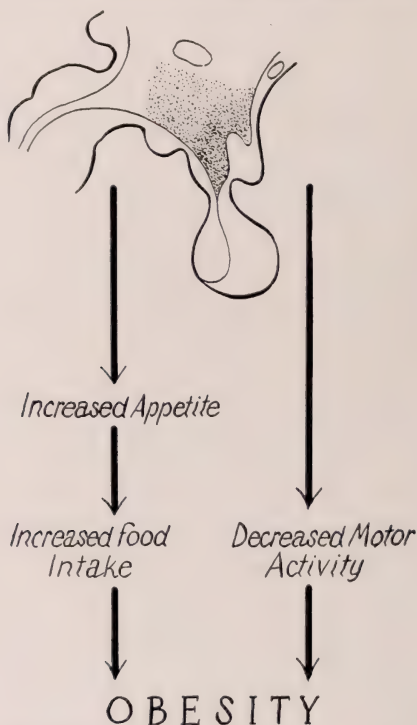


FIG. 8. Diagram supplementing discussion on obesity.

follows increased ingestion of food, sometimes with and sometimes without a relative decrease in the activity of the subject. The increased ingestion of food resulting from hypothalamic injury is often referred to as *hypothalamic hyperphagia*. Also, lesions in the region of the tuber cinereum are associated with decreased motor activity. *It is clear that hunger (or excessive desire for food) and decreased motor activity are often manifestations of a hypothalamic disorder.*

*Basal metabolism: hormonal and hypothalamic factors*

The maintenance of normal thyroid function depends on a well regulated yield of thyrotropic hormone by the anterior pituitary. In provoking greater activity of the thyroid this hormone brings about a greater output of the thyroid hormone. It is capable, however, of other effects and in excess may be responsible for the exophthalmos following thyroidectomy for Graves' disease. Retention of periorbital tissue fluids may be the cause of this form of exophthalmos.

For balanced activity of the thyroid it is essential that there be not only an adequate amount of thyrotropic hormone, but that the quantity be kept within certain limits. Limitation of the quantity of effective thyrotropic hormone is achieved in part by the action of thyroid hormone in the circulating blood which blocks the effect of the thyrotropic hormone. By acting also on the hypophysis the thyroid hormone suppresses the overproduction of thyrotropic hormone. Also, the thyroid hormone exercises an inhibitory influence upon the thyroid cells, reducing their secretory activity.

Basal metabolism, which is controlled by the direct action of the thyroid, is apparently also under the regulating influence of the hypothalamus. The influence of the hypothalamus on the cervical sympathetic nerves is such as to permit the assumption that within the hypothalamus there are nuclei which may serve as centers contributing to the control of basal metabolism. This action upon the gland is probably not mediated by fibers terminating directly in the secretory parenchyma but by action of the sympathetic nervous system on the vascular supply to the gland, causing changes in the blood flow through the gland and thereby varying the degree of its activity. Hypothalamic control of thyroid function may also be mediated through alterations in the secretion of the anterior pituitary.

The interrelationships discussed in the foregoing are illustrated in Figure 9. It is likely that a lesion in the hypothalamus may effect changes in basal metabolism, either by influencing the pituitary secretion of thyrotropic hormone or by influencing the secretion of the thyroid itself. It may be concluded that (1) *hypothyroidism may be a manifestation of hypopituitarism*, (2) *hyperthyroidism may be a manifestation of pituitary hyperfunction*, and (3) *hypothyroidism or hyperthyroidism may be manifestations of a hypothalamic disturbance*.

*Genital development and functions with particular reference to the gonadotropic hormones*

The anterior pituitary is responsible for the elaboration of several hormones (or hormone fractions) which have the gonads as their targets. Figure 10 illustrates graphically their assumed physiologic actions.

In the female, F.S.H. (follicle stimulating hormone) acts upon the ovaries to stimulate follicle growth. Follicle growth is accelerated when F.S.H. is augmented by the effect of small amounts of luteinizing hormone (L.H.) leading finally to rupture of the follicle. The follicle throughout its existence liberates

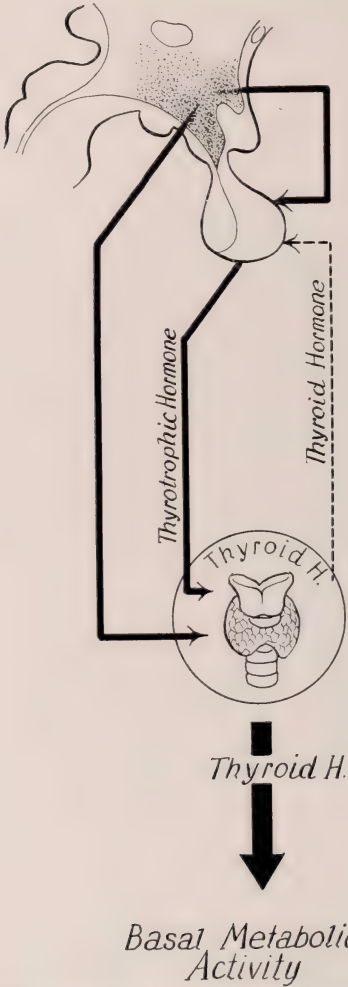


FIG. 9. Diagram supplementing text dealing with Basal Metabolism. (Interrupted lines denote inhibition; solid lines, activation.)



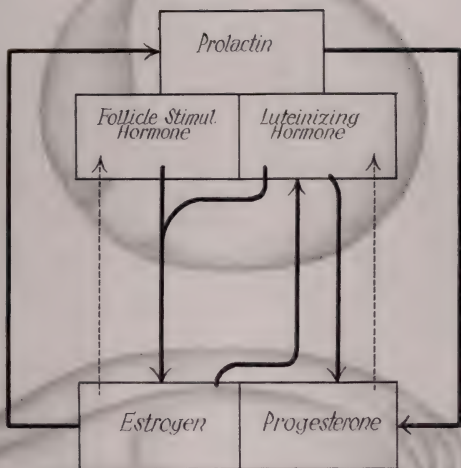


FIG. 10. Diagram supplementing text on gonadotrophic hormones. (Interrupted lines denote inhibition; solid lines, activation.)

estrogen which acts upon the anterior pituitary to depress the secretion of F.S.H. (follicle stimulating hormone) and increase secretion of luteinizing hor-

none. The luteinizing hormone (L.H.), having contributed its share to the maturation of the follicle, promotes its rupture and luteinization. The corpus luteum in turn secretes progesterone which acts upon the anterior pituitary to depress the formation of L.H. When L.H. decreases in amount, the production of F.S.H. again increases and a new cycle is initiated.

*Prolactin*, a third hormone with influence on sex characteristics or function, is effective mainly in prolonging the existence of the corpus luteum, particularly during the period of pregnancy. Estrogenic substances produced by the placenta during pregnancy act upon the pituitary to stimulate its production of prolactin, thus, perpetuating the corpus luteum which, by continued secretion of progesterone, maintains the uterus in a gestational state.

Of no little significance is the fact that the F.S.H. and L.H. are produced and play an active role also in the male. The F.S.H. with the seminiferous tubules as the target stimulates their growth and activity in the proper maturation of spermatozoa. The L.H. acts upon the interstitial cells and thus provokes production of androgens (testosterone).

*The foregoing seems to indicate that underdevelopment, overdevelopment or involution of sex organs is a frequent manifestation of a disturbance in the hypophysio-hypothalamic mechanism.* The anterior pituitary hormones have the gonads as one of their targets. Their action is known to provide a regulating influence over the normal development of sex organs and sex features. When the balanced yield of these hormones is disturbed underdevelopment or overdevelopment of the sex organs are known to occur. Here again the hypothalamus, through its direct or indirect association with the pituitary, exercises an important influence over the gonadal functions with results similar to those traceable to normal or abnormal functions of the pituitary.

That a hypothalamic disorder may result in genital dystrophy was experimentally established by the comprehensive studies of P. E. Smith and is substantiated by clinico-pathologic observations. Moreover, alterations in the hypothalamus (more correctly in the floor of the third ventricle) such as found in hydrocephalus caused by obstruction in the aqueduct are often associated with precocious development of sex organs (macrosomia genitalis).

#### *Water balance and the hypophysio-hypothalamic unit*

A balanced intake and output of fluids, essential for the proper electrolyte content of body fluids, is maintained by both the hormonal yield of the neuro-hypophysis and the regulating function of the hypothalamus. The posterior lobe of the pituitary yields by extraction an antidiuretic hormone. In all probability, the hormone is a product of the pituicytes. The antidiuretic hormone may also be secreted by neuro-ectodermal cells in the pituitary stalk and cells in the hypothalamic nuclei (tuber cinereum and supra-optic nucleus). The supra-optic nucleus, as already mentioned, is in direct connection with the posterior lobe of the hypophysis by means of the supra-optico-hypophysial tract. When the supra-optic nuclei alone are destroyed there is a loss of cells capable of secreting the antidiuretic hormone since the posterior lobe, which it innervates, loses its function. Destruction of the posterior lobe of the hypoph-

ysis, stalk, and tuberal region of the hypothalamus indicates a loss of the greater part of the secretory elements and diuresis is the result. It has been shown in experimental animals that the diuresis may be markedly ameliorated if the anterior lobe of the hypophysis is removed. Removal of the thyroid has an ameliorative effect on the diuresis and raises the question as to whether the thyroid hormone, through its influence on general metabolism, is not the chief determinant factor in diuresis. Depriving the thyroid of the thyrotropic hormone may, therefore, account for the improvement when the anterior lobe of the hypophysis is removed. It is also likely that at least part of the amelioration of symptoms with hypophysectomy depends upon the loss of stimulation of the cortex of the adrenals by the adrenocorticotrophic hormone and consequent decrease in adrenal cortical activity. The interrelationship is in part demonstrated in Figure 11.

*Thus, it may be said that a lesion, primary or secondary, affecting the anterior or middle hypothalamic nuclei in the presence of adequately functioning anterior pituitary and other endocrine glands may cause signs and symptoms of diabetes insipidus; and that posterior pituitary hypofunction, in the presence of sufficiently active anterior lobe and other properly functioning endocrine glands, may provoke diabetes insipidus, provided that the secretory elements of the stalk and hypothalamus are also injured or deficient and incapable of compensating for the deficiency of the neurohypophysis.*

#### *Growth: hormonal and hypothalamic factors*

The existence of a growth hormone was for a long time a subject of controversy. It was maintained by some investigators that the growth stimulating properties of the anterior hypophysis are not represented by one single hormone—intimating that no such hormone exists. In their opinion the anterior hypophysis promotes growth through the effect of several of its hormones acting synergistically. However, it was demonstrated that anterior hypophyseal extracts containing (as measured by side effects) only an extremely small amount of other derivatives of the anterior pituitary still appreciably stimulate growth. Recently a purified growth hormonal principle has been isolated.

In view of this, it is assumed that a growth hormone is secreted by the anterior pituitary; its optimum action probably is only attained when it is properly balanced with products of other glands of internal secretion. The growth hormone stimulates protein anabolism, skeletal and visceral growth, and results in weight increase and structural enlargement.

Impure growth stimulating anterior pituitary extracts, when administered to animals over sufficiently long periods, were found to provoke permanent diabetes mellitus. This aroused the suspicion that a diabetogenic hormone, possibly identical with the growth hormone, was elaborated by the anterior pituitary. This view found some support in the observation that partially depancreatized animals, when given a relatively pure growth hormone, tended to manifest an increase in the glycosuria.

The exact mechanism whereby a permanent diabetes mellitus is produced by anterior pituitary extracts is not known. It is possible that one primary

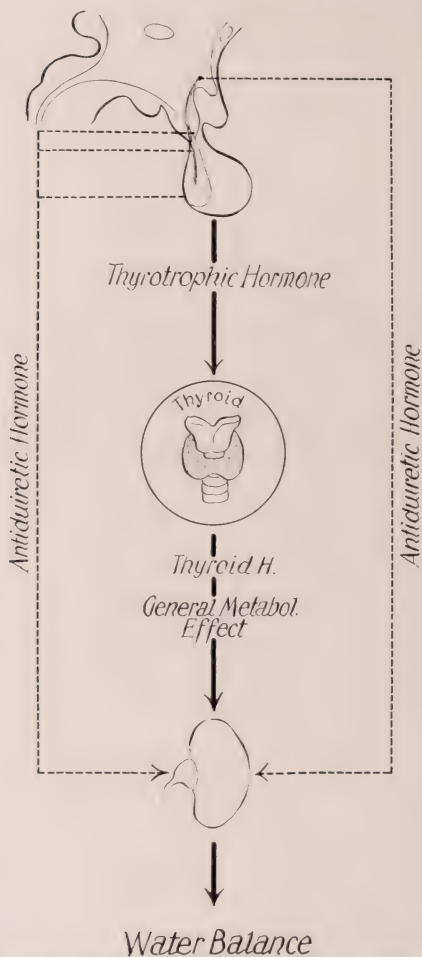


FIG. 11. Diagram supplementing text on water balance. (Interrupted lines denote inhibition; solid lines, activation.)

action is a stimulation of the adrenal cortex with resultant hyperglycemia. This leads early to stimulation and finally to exhaustion of the *beta* cells of the

islands of Langerhans and the diabetic state. However, it must be borne in mind that Houssay has been able to demonstrate a diabetogenic action of pituitary extract in the absence of the adrenal glands indicating that a non-adrenal mechanism may also exist which produces this type of diabetes.

A clear evaluation of the action of the growth hormone is made difficult by the significant role of thyroid hormone and testicular interstitial cell hormones (testosterone) as growth stimulating factors. Each of these hormones contributes substantially toward the development and formation of the organism by its individual action and synergically by potentiating the action of the growth hormone. The presence of an excess of adrenal cortical steroids may disturb growth by increasing protein catabolism. Similarly, derangement of thyroid function by shifting the metabolic rate excessively in either direction may affect growth.

The androgens and estrogens have a more direct influence on growth. Testosterone contributes directly toward development and formation of the skeleton, the larynx and probably other tissues, and to closure of the epiphyses when the general glandular metabolic balance is properly maintained. Estrogen, on the other hand, tends to inhibit certain of these changes, and general growth by favoring epiphyseal closure and possibly by suppressing pituitary hormone secretion of importance in growth stimulation.

The complexity of these interrelationships can not be overemphasized (fig. 12). For example, the inhibitory effect of excess adrenocorticotrophic hormone on growth may be questioned, as it may be more apparent than real: overproduction of this hormone may necessitate curtailed production of other essential hormones or administration of excess of this hormone may result in suppressed function of an otherwise active pituitary gland.

The hypothalamic influence on growth, in the sense of a direct contribution to such control, is still in need of substantiating direct observation other than recognition that the hypothalamus plays a significant role in the dystrophic state *macrosomia genitalis*. The question arises whether the concomitant overdevelopment of the sexual characters and somatic musculature is to be considered as a manifestation of a disorder of the hypothalamus or (as it seems more probable) that both the hypothalamus and the pituitary are implicated in the production of this syndrome.

*The adrenocortical activity in relation to the hypophysis  
and hypothalamus*

The hormone most essential for the normal function of the adrenal cortex is the adrenocorticotrophic hormone of the anterior pituitary. In its absence it is found that cortical atrophy takes place. Moreover, if one gland is experimentally removed the cortex of the other adrenal undergoes hypertrophy. It would seem that under such a condition the adrenocorticotrophic hormone, now in relative excess in view of the massive reduction in adrenal cortex, provokes a compensatory hypertrophy of the remaining adrenal cortex.

Extraction of the adrenal cortex yields a number of hormones (or hormone fractions). Their most significant functions suggest their grouping (fig. 13)



into those contributing to: 1) increased protein catabolism, gluconeogenesis and muscle efficiency; 2) regulation of electrolyte balance; 3) kidney function and maintenance of life (specific action unknown); and 4) those contributing to balanced sex development. These have been extracted from the adrenal cortex, but it is not yet certain whether they are a product of the adrenals or only stored there.

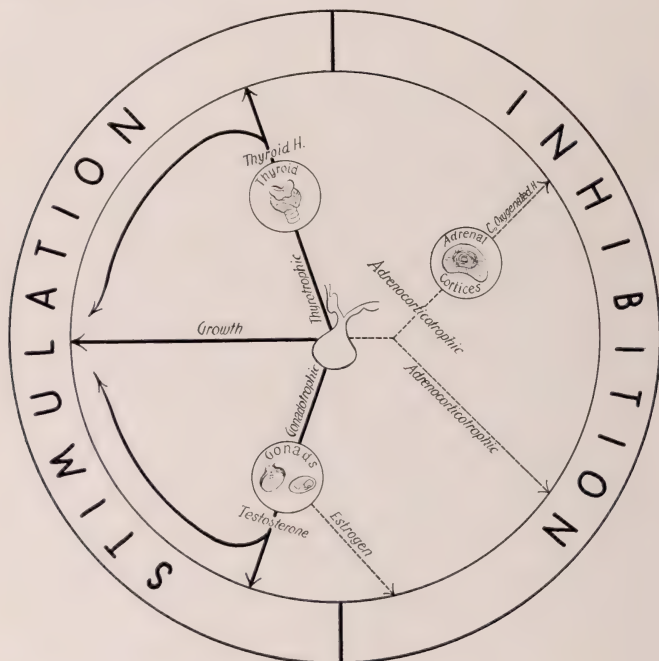


FIG. 12. Diagram supplementing text on growth

The hormones which promote gluconeogenesis (by increased protein catabolism) are commonly known as the "sugar hormones." These are  $C_{11}$  oxygenated corticosterones; in their action they are opposed to that of insulin; they increase glycogen deposition in the liver and muscle and contribute to muscular efficiency. All of these effects can be brought about in animals with intact adrenals by the administration of adrenocorticotrophic hormone. An excess of these hormones has been suggested as a causative factor in the occurrence of

insulin-resistant diabetes mellitus, such as encountered in Cushing's syndrome and in acromegaly.

The electrolytic balance is regulated by the desoxycorticosterone fractions of the adrenal cortex extracts. Administration of this substance causes sodium retention and potassium excretion, the retention of water and a probable rise in blood pressure. Administered in excess, this substance may provoke certain paradoxical effects, for example, diuresis.

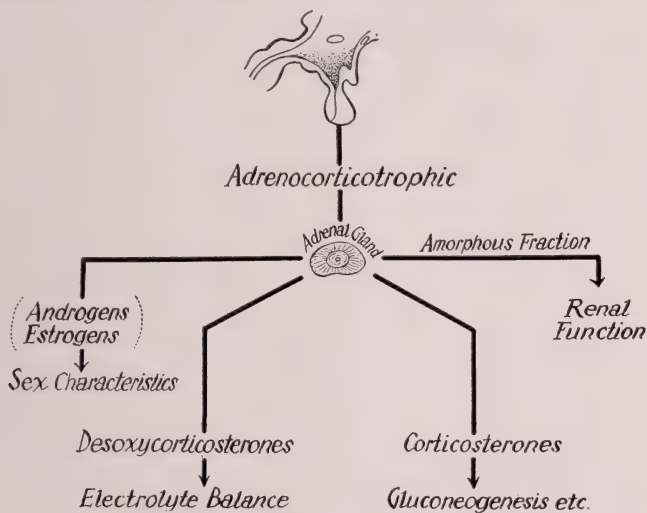


FIG. 13. Diagram supplementing text on adreno-cortical activity.

Preservation of life is apparently dependent on the amorphous fraction, extractable from the adrenal cortex (containing none of the aforementioned corticosterones or desoxycorticosterones). This is demonstrated in adrenalectomized animals over long periods. Kendall believes that there may be a primary, direct control of renal function by this group of adrenal substances.

Recently it has been shown that adrenal cortical hormone may exert a lytic effect on cells of the lymphocyte series. In this connection it is interesting that in the presence of hypopituitarism, where adrenal cortical function is also probably reduced, a relative blood lymphocytosis is found.

The hypothalamus participates in the activity of the adrenals to some, and probably a limited, extent. This action is most obvious in the diabetes insipidus syndrome and less so in the Cushing's syndrome. It is not improbable that both the hypothalamus and the adrenals join action in some biologic adapta-

tions. How this is brought about is still open to question. Hormone production in the hypothalamus, if accepted, could explain it as could also the more indirect action of neural transmission of hypothalamic influences.

*It may be concluded, then, that hypoadrenocorticism, with all or many of the symptoms and signs noted in Addison's disease, may result from hypopituitarism.*

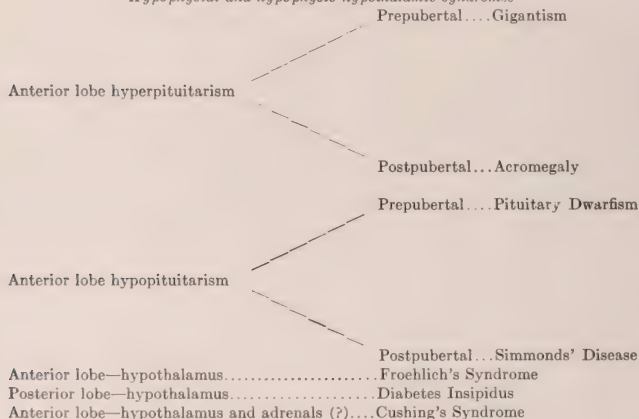
## SECTION II

### SYNDROMES OF HYPOPHYSIO-HYPOTHALAMIC DYSFUNCTION

There are seven rather well defined syndromes which have been correlated with hypophysio-hypothalamic dysfunction. These clinical syndromes are tabulated in Chart IV.

#### CHART IV

##### *Hypophysial and hypophysio-hypothalamic syndromes*



#### GIGANTISM

##### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

#### I. Symptoms and signs

- A. Skeletal over-growth occurring at the time the epiphyses are open, resulting in an increase in length of long bones; mild acromegalic changes may develop after closure of epiphyses occurs;
- B. Early (transient) sexual maturity followed by loss of sexual characteristics and functions;
- C. Early (transient) muscular over-development followed by asthenia and cachexia.

#### II. Anatomico-physiologic implications

- A. Anterior lobe of pituitary—Excessive growth and gonadotrophic hormones followed by exhaustion of these hormones.

#### III. Character of lesion

- A. Eosinophile hyperplasia, adenoma, or adenocarcinoma of anterior lobe of the pituitary.

## IV. Therapy

- A. Surgery;
- B. Radiotherapy. } not too successful

## ACROMEGALY

## SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

## I. Symptoms and signs

## A. Early phase—

1. Skeletal and visceral over-growth;
2. Hypergonadism with accentuation of secondary sex characteristics with increased libido and potency;
3. Hyperglycemia and glycosuria;
4. Some or all manifestations of hyperthyroidism.

## B. Intermediate phase—

1. Persistent skeletal and visceral over-growth;
2. Recession (to normal or below) of primary and secondary sex characteristics;
3. Hyperglycemia and glycosuria may persist;
4. Disappearance of signs of hyperthyroidism or appearance of hypothyroid features;
5. Polyuria and polydipsia.

## C. Late phase—

1. Retention of skeletal and visceral over-growth, without further augmentation;
2. Hypogonadism with loss of libido and potency, amenorrhea, etc.;
3. Glycosuria and hyperglycemia may persist;
4. Hypothyroidism;
5. Asthenia, cachexia, increased susceptibility to infections, (hypoadrenocorticism).

Note: This terminal stage is essentially one of panhypopituitarism and merges into the clinical picture of Simmonds' Disease. It is the result of exhaustion of the secretory cells and in some cases of destruction of the hypophysis itself.

## II. Anatomico-physiological implications

## A. Early phase—

1. Anterior lobe of pituitary—Over-secretion of growth-hormone due to eosinophilic cell hyperplasia. Over-secretion of other hormones, either because these are products of the eosinophile cells or because over-activity of these cells stimulates other cell types to over-production.

## B. Intermediate phase—

1. Anterior lobe of pituitary—Continued over-secretion of growth hormone. Decrease in secretion of other anterior pituitary hormones;
2. Posterior lobe of pituitary—Compression may result in insufficient anti-diuretic hormone.

## C. Late phase—

1. Anterior lobe of pituitary—Deficiency of all hormones;
2. Posterior lobe of pituitary—Insufficiency of anti-diuretic hormone.

## III. Character of lesion

- A. Eosinophile adenoma of pituitary which progressively enlarges; eosinophile cells lose their granules, assume character of chromophobe cells, subsequently cystic degeneration takes place.

## IV. Therapy

- A. Surgery in selected cases may result in improvement;
- B. Radiotherapy.

Gigantism and acromegaly are sufficiently similar clinically and pathologically to be considered variations of a single entity. Both are associated with

hyperfunction of the eosinophile elements of the pituitary. For this reason we shall limit ourselves to a description of the clinical features of gigantism and present a clinical example only for acromegaly.

Eosinophile tumors of the pituitary are most commonly encountered in acromegaly. However, the tumors of acromegalic patients do not always reveal readily recognized eosinophile cells. This is explained by the probability that either the parent cells (chromophobes) have not become fully differentiated, or else the eosinophile cells have become exhausted by their hyperactivity so that the secretory granules are present in so few numbers as to be found only with difficulty. Whatever the process may be, it seems fairly well established clinically that there is first a period of anterior pituitary hyperactivity, ultimately followed by diminished activity in both gigantism and acromegaly. The following case illustrates some of the features of the disease.

*Illustrative case 1. History.* (Adm. #402097; P. M. #10160) The patient, a man aged 46 years, was brought to the hospital in a state of semi-stupor. Five years earlier (when the patient was 41 years of age) disproportionate increase in size of the hands, feet, forehead and jaw, together with considerable change in facial appearance, was first noted. He also voided large quantities of urine very frequently, day and night. Diabetes mellitus was diagnosed and insulin with dietary restriction was prescribed. The patient did not follow medical advice and sought no further medical care. In the course of time he became increasingly somnolent and his vision gradually became impaired. His sexual habits remained unchanged for the first four years of his illness, but then there set in a decrease in libido which soon progressed to complete impotence. At the end of the fourth year of his illness there was no further overgrowth and the polyuria decreased. He became, however, progressively more somnolent and continued to gain weight steadily.

*Examination.* The patient was an obese and pallid male with a markedly enlarged skull, coarse features and disproportionately large extremities (fig. 14). The skin of the face was thickened, the eyelids were puffy. There was cyanosis of the nail beds and there was slight incurvation of the finger nails. There was feminine distribution of body hair and facial hair was scanty. The pupils were irregular but equal and reacted sluggishly to light and in accommodation. Vision on gross examination was found to be less acute in the right eye than in the left. Confrontation visual field studies revealed no defect. There was slight peripapillary edema. The tongue was large and thick, the teeth were widely spaced. The chest was large, especially in the anteroposterior diameter. There was moderate enlargement of the heart to the left and a systolic murmur was audible at the base. There was considerable abdominal fat. The testes were small and soft.

*Laboratory data.* The urine showed a faint trace of albumin, 3+ sugar and 1+ acetone. The blood sugar was 240 mg. per cent. The cerebrospinal fluid was under an initial pressure of 230 mm. of water; after the withdrawal of 10 cc. of the fluid the pressure dropped to 170 mm. of water. The fluid was slightly xanthochromic and contained sugar 105 mg., chlorides 690 mg. per cent and total protein 4 mg. per cent; the Wasserman test was negative.

*Course.* During the first day in the hospital the patient was semi-stuporous but could be easily aroused. His breathing was Cheyne-Stokes in type and he complained of severe headache. He was given 5 per cent glucose in saline to which were added 10 units of insulin for every 200 cc. of fluid administered. His condition remained unchanged throughout the night but the following day he declined rapidly and died.

*Necropsy findings. General.* There was generalized splanchnomegaly. The thyroid was hyperplastic and contained a colloid adenoma. The thymus was hypertrophied. The mesenteric lymph nodes and the lymphoid tissue of the gastro-intestinal tract were hyperplastic. There was hypertrophy and dilatation of the heart with slight interstitial mitral



valvulitis and moderate myocardial fibrosis. The coronary arteries were narrowed and sclerosed. The pulmonary arteries were atheromatous. The liver, spleen and kidneys were congested. There was pulmonary emphysema. Multiple cortical cysts of the kidneys were present and there was nephrolithiasis of the right kidney. Lipomatosis of the pancreas, multiple mucosal erosions of the esophagus, diverticulosis of the colon and a small fibroma of the ileum were also observed.



FIG. 14. Case illustrating fairly well developed features of acromegaly

*Brain.* A cone-shaped, fleshy, smooth mass of tissue protruded from the sella turcica below (fig. 15), attached to the tuber cinereum above by a thin stalk. The mass was half an inch in diameter at the base and one inch high. The mass of tissue had enlarged the interpeduncular space, pressed upward against the floor of the third ventricle and flattened the optic chiasm.

Section of the brain revealed no internal hydrocephalus or evidence of cerebral edema.

*Microscopic anatomy.* Sections of the pituitary neoplasm revealed it to be an eosinophilic adenoma. Many multi-nucleated giant cells were present. Cells with cytoplasmic granules predominated; special staining methods revealed the granules to be acidophilic. At the periphery of the tumor there were numerous acini recalling the structure of the anterior lobe of a normal pituitary body. This was apparently that part of the original gland which had been compressed by the growth of the tumor.

*Comment.* The foregoing case presented features and manifestations of acromegaly characteristically of both the intermediate and late phases.

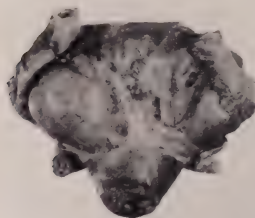


FIG. 15. Pituitary tumor in a case of acromegaly  
PITUITARY DWARFISM

#### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

- I. Symptoms and signs
  - A. Retardation or inhibition of growth;
  - B. Retardation or inhibition of development of the external genitalia. In severe cases, there may be associated under-development of secondary sex characteristics and such dysfunction as amenorrhea, impotence and sterility;
  - C. Obesity, diabetes insipidus, low basal metabolic rate (less common features);
  - D. Typical facies—"doll face" with "geroderma" (fine, wrinkled skin).
- II. Anatomico-physiologic implications
  - A. Anterior lobe of pituitary—
    1. Insufficient growth hormone;
    2. Insufficient gonadotropic hormone.
- III. Character of lesion
  - A. Expanding lesions which interfere (by compression) with the activity of the anterior lobe of the pituitary;
  - B. Congenital hypoplasia, or absence, of secretory cells of the pituitary.
- IV. Therapy
  - A. Hormones (anterior pituitary and gonadal hormones), when well balanced, may result in improvement.

*Illustrative case 2. History.* (Adm. # 383704) A man, aged 20 years, entered the hospital because of retardation of physical development since the age of 13.

*Examination.* The patient was small (height 55 inches, weight 86½ pounds), and his voice was high-pitched. He had no axillary and pubic hair, his skin was brown and dry. The genitalia were markedly underdeveloped. The right pupil was larger than the left, a right facial weakness of supranuclear type was present, and there was a beginning optic atrophy of the right disc and well developed optic atrophy of the left. Perimetry showed the visual fields to be normal. Visual acuity was only slightly reduced on both sides. His blood pressure was 86 systolic and 50 diastolic.

*Laboratory data.* The glucose tolerance curve was flat. X-rays of the skull showed an erosion of the floor and posterior clinoid processes of the sella turcica. Examination of the long bones showed epiphyseal development normally found in persons of 14 to 15 years of age.

*Course.* He was discharged to receive radiotherapy and organotherapy. About 6 years later a craniotomy was done because of progression of signs of pressure on the optic chiasm, and a cystic hypophyseal duct tumor (craniopharyngeoma) was removed. About 18 months after this operation his general physical status was unchanged. There was bilateral anosmia, bitemporal hemianopsia, bilateral primary optic atrophy, greater on the left and weakness and incoordination of the left upper extremity. He complained of intermittent attacks of dizziness and frontal headache. He also reported to his private physician (J. H. G.) that he became very sensitive to alterations in temperature; his body temperature would rise or drop with similar changes in the atmospheric temperature. There was sufficient clinical and laboratory evidence to indicate recurrence of the cystic tumor and re-operation was advised. This was refused by the patient. About two years later word was received from another hospital that the patient had expired. The post mortem examination revealed "benign hemorrhagic cyst, involving pituitary with destructions; infantilism; decubitus ulcers; suppurative arthritis, right knee."

*Comment.* In this instance there is strong probability of a joint implication of both pituitary and hypothalamus. The post mortem finding indicating destruction of the pituitary, while not proving a pre-existing disease of the gland, does not exclude its involvement during the early phase of the disease, the dwarfism pointing to such a likelihood. The polydipsia and polyuria and the later development of a poikilothermia indicate a hypothalamic disorder.

### SIMMONDS' DISEASE

#### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

- I. Symptoms and signs
  - A. Cachexia and asthenia;
  - B. Low basal metabolic rate and other features of hypothyroidism;
  - C. Involution of primary and regression of secondary sex characteristics.
- II. Anatomico-physiologic implications
  - A. Anterior lobe of pituitary—Insufficient secretion of all its hormones.
- III. Character of lesion
 

<ol style="list-style-type: none"> <li>A. Post-partum hemorrhage or thrombosis with necrosis;</li> <li>B. Neoplastic lesions, primary or metastatic;</li> <li>C. Inflammatory lesions (gumma, tuberculoma);</li> <li>D. Trauma (skull fracture).</li> <li>E. Fibrosis</li> </ol>	}	of anterior lobe of hypophysis
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- IV. Therapy
  - A. Hormones (thyroxin, testosterone and adrenal cortical hormone), when properly balanced, may result in improvement.

*Illustrative case 3. History.* (P. M. #6970) A woman, aged 53 years, was admitted to the hospital complaining of wasting and general weakness. She had been well until a year previously when she began to show evidence of lowered resistance to infections. She became subject to repeated upper respiratory infections, developed a persistent cough

and lost weight steadily. The loss of weight and strength advanced rapidly. In the course of the year she lost about 38 pounds. Three weeks prior to admission she had a gastrointestinal upset with crampy abdominal pain, diarrhea, vomiting, and fever which lasted about a week.

*Examination.* The patient was extremely emaciated and cachectic with almost complete loss of subcutaneous fat tissue (fig. 16). She weighed about 60 pounds. Several



FIG. 16. Case of pituitary cachexia

impetiginous lesions were scattered over the face. There was slight generalized pigmentation of the skin. The eyes were sunken. Most of the teeth were missing, the few remaining were carious. The breasts were atrophic, the abdominal wall was thin and atrophied. The extremities were markedly wasted; edema of the feet extended to just above the ankles. The blood pressure was 112 systolic and 90 diastolic.

*Laboratory data.* The hemoglobin was 58 per cent; the red blood count was 3,200,000. A Rehfus test showed complete achlorhydria after histamine. Roentgenology revealed no abnormalities of the chest or G.I. tract. Blood chemistry was normal. Tuberculin test was negative.

*Course.* Throughout her hospital stay the patient's weakness kept her confined to her bed. On the sixth hospital day she suddenly lapsed into coma and could not be roused, even by painful stimuli. Her breathing became slow and shallow, she perspired profusely, the pulse and respirations became progressively weaker and she died within a few hours.

*Necropsy findings.* *General.* All of the visceral organs were atrophied and there was

general anasarca. There was pulmonary emphysema, pulmonary edema and calcified tuberculosis of the right lower lobe. Ulcers of the esophagus and small intestines were present. The mesentary lymph nodes were calcified. Moderate arteriosclerosis of the coronary arteries was present.

*Brain.* There were no significant changes in the brain.

*Pituitary.* The anterior lobe was markedly fibrotic, there were very few intact parenchymatous cells.

*Comment.* The changes in the pituitary gland are typical of those found in Simmonds' disease.

## FROEHLICH'S SYNDROME

### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

#### I. Symptoms and signs

- A. Obesity with selective deposition of fat;
- B. Genital hypoplasia;
- C. Polyuria and polydipsia; other vegetative manifestations of hypothalamico-hypophyseal dysfunction may or may not be present.

#### II. Anatomico-physiologic implications

##### A. Hypothalamus—

1. Genital hypoplasia;
2. Obesity resulting from imbalance of caloric intake and energy expenditure;

##### B. Anterior lobe of pituitary—

1. Insufficient gonadotrophic hormone [hypoplasia or atrophy of gonads with resultant under-development of external genitalia (pre-pubertal), atrophy of genitalia, decline in libido, amenorrhea, impotence, change in amount and distribution of hair (post-pubertal)];
2. Insufficient growth hormone (retardation in growth); (occasionally augmented prepubertal growth due to delayed closure of epiphysis).

##### C. Gonads—[selective (feminine) deposition of fat].

#### III. Character of lesion

- A. Chromophobe adenoma; } Implicating both the hypothalamus and the anterior
- B. Suprasellar tumor. } lobe of the pituitary.

#### IV. Therapy

- A. Hormones are of little value because the hypothalamic involvement plays the dominant role in the production of the symptoms, but testosterone in male, estrogen in female are of some benefit while administration of the hormone is continued.

- B. Surgery, when practicable, may result in some improvement.

*Illustrative case 5. History.* (Adm. #350459; P. M. #8743) A man, aged 46 years, entered the hospital complaining chiefly of failing vision of six years' duration. His early development was apparently normal but at adolescence it was noted that his genitalia were small, his left testicle incompletely descended, and his axillary and pubic hair was scanty and of feminine distribution. He was sexually active until he reached 32 years of age. At this time his libido and potency decreased rapidly and finally disappeared entirely. At the age of about 40 years he noted that vision in his right eye was failing and he began to have recurrent mild right frontal headaches. Four years later, at the age of 44, he became aware of impaired vision in the left eye. The loss of vision progressed so that six weeks preceding his admission to the hospital he was no longer able to read; attempts to do so resulted in dizziness and increased severity of the right frontal headaches.

*Examination.* The patient was small and obese with feminine distribution of fat. His body hair was scanty and also of feminine distribution. His teeth were carious. The abdomen protruded. The left testis was not present in the scrotal sac. There was hyposmia on the right, the right palpebral fissure was larger than the left and the pupils were



irregular and unequal, the right being larger than the left. The right pupil reacted sluggishly to light; the consensual light reflex was absent when light was thrown on the right eye, but present when thrown on the left. There was bilateral optic atrophy, greater on the right. No vision for light was present in the right eye and the left eye retained vision only in an area confined to the nasal visual field. There was a left facial asymmetry.

*Laboratory data.* Routine studies of blood and urine revealed no significant changes. Glucose tolerance test was normal.

*Course.* Two weeks after he entered the hospital craniotomy was performed. A tumor was found lodged anterior to the optic chiasm; it bulged above the level of the sella pushing the right optic nerve laterally. Partial removal of the mass by curettage and aspiration revealed its capsule to extend into the sella. After the operation the patient was restless, disoriented, and incontinent. His temperature rose steadily. Twenty-four hours later he improved for a brief time, but he then became somnolent and his temperature continued to rise. Despite supportive treatment and attempts to decrease his elevated cerebrospinal fluid pressure, on the second post-operative day, the patient's temperature rose to 108°F. and he died.

*Necropsy findings.* The interpeduncular region of the brain was occupied by a reddish, irregular, somewhat cystic tumor mass measuring about 4 cm. in diameter (fig. 19). It was adherent to and appeared to arise from the interpeduncular region and extended rostrally under the right frontal lobe.

The right frontal lobe was soft. The remainder of the brain and vessels were negative.

On sectioning of the brain the tumor mass was seen to separate the temporal lobes and raise the floor of the third ventricle and the anterior portion of the right lateral ventricle. It had caused pressure softening of the floor of the third and right lateral ventricles with similar softening in the adjacent portions of the thalamus. The ventricular system was dilated and displaced to the right and upwards. More anteriorly the tumor invaginated the under surface of the right frontal hemisphere. The tumor was well encapsulated and did not directly invade the brain at any point.

*Microscopic anatomy.* There was chronic productive leptomeningitis and cerebral arteriosclerosis. The pituitary was represented by the tumor mass which consisted of poorly staining cells with dark nuclei characteristic of a chromophobic adenocarcinoma.

*Comment.* In this instance, though the tumor was primary in the pituitary, it caused almost complete destruction of the hypothalamus, the structure which is regarded as essential in controlling the development of sexual characteristics. The long clinical history (12 years) suggests that a chromophobe adenoma underwent carcinomatous change in this case.

## DIABETES INSIPIDUS

### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

- I. Symptoms and signs
  - A. Polyuria—Excessive output of urine of fixed low specific gravity;
  - B. Polydipsia—Excessive thirst with intake of unusually large quantity of fluid; occasional polyphagia.
- II. Anatomico-physiologic implications
  - A. Hypothalamus—Especially, supra-optic nuclei and hypothalamico-hypophyseal tract;
  - B. Neurohypophysis—Reduction of anti-diuretic hormone;
  - C. Anterior lobe of hypophysis—Its maintained function together with normal activity of the thyroid (and possibly also that of the adrenals) is essential for the development of the syndrome.
- III. Character of lesion
  - A. Neoplastic (hypothalamic, supra-sellar, pituitary, third ventricle, and others which secondarily affect the hypothalamus);

- B. Inflammatory [gumma, tuberculoma, encephalitis (in same localization as above)];
- C. Trauma (fracture of the base of the skull).

#### IV. Therapy

- A. Anti-diuretic hormone (pitressin);
- B. Radiotherapy;
- C. Surgery.

*Illustrative case 4. History.* (Adm. #233880; P. M. #4432) A man, aged 48 years, was hemiplegic since infancy and mentally retarded since childhood. Five months before admission to the hospital he began to lose his eyesight and was troubled by excessive thirst and frequent urination. He was given pituitary extract and responded to treatment with slight improvement in vision and decided decrease of thirst and urination. Interruption of treatment five weeks after it was begun resulted in immediate return of his symptoms. Resumption of pituitary extract failed to produce the former amelioration of symptoms.

*Examination.* The significant positive findings were left-sided hemiplegia, bitemporal hemianopsia, pallor of both optic discs and unequal pupils which reacted poorly to light.

*Laboratory data.* The blood and cerebrospinal fluid gave a strongly positive Wassermann reaction.

*Course.* The bitemporal hemianopsia, polydipsia and polyuria suggested the presence of a pituitary tumor. The patient's condition declined rapidly and he died before operation could be performed.

*Necropsy findings.* The brain disclosed a tertiary syphilitic lesion, gummatous in character, in the floor of the third ventricle. The gumma in part replaced the tuber cinereum (fig. 17).

*Comment.* This case merits particular attention, for it is a rare instance exhibiting a discrete lesion (gummatous) in the tuber cinereum, a structure crowded with the important centres (nuclei) controlling vegetative functions.

### CUSHING'S SYNDROME

#### SYNOPTIC OUTLINE OF CLINICAL AND ANATOMICO-PHYSIOLOGIC FEATURES

- I. Symptoms and signs
  - A. Obesity ("Buffalo type") limited to head and trunk;
  - B. Purple striae of skin;
  - C. Hypertension, erythremia, and plethora;
  - D. Osteoporosis;
  - E. Hirsutism (in female);
  - F. Loss of sexual function (masculinization of female, feminization of male);
  - G. Hyperglycemia, glycosuria.
- II. Anatomico-physiologic implications
  - A. Pituitary basophile cells; infundibulum; hypothalamus(?);
  - B. Many of the symptoms are traceable to adrenal cortical hyperactivity.
- III. Character of lesion
  - A. Basophile cell adenoma of pituitary (anterior lobe?);
  - B. Adrenal cortical adenoma, adenocarcinoma or simple hyperplasia;
  - C. Thymic tumor;
  - D. Hypothalamic lesions.
- IV. Therapy
  - A. Radiotherapy to pituitary or adrenals or both;
  - B. Surgery (removal of hypertrophied adrenal, thymic tumor);
  - C. Hormones (of doubtful value).

*Illustrative case 6. History.* (Adm. #388617; P. M. #9831) A young man, at the age of 23 years, was discovered to have hypertension, although he was otherwise apparently well. About two and a half years later he began to put on weight and gained forty pounds in the next six months. The obesity was limited to the trunk, sparing the arms and legs.

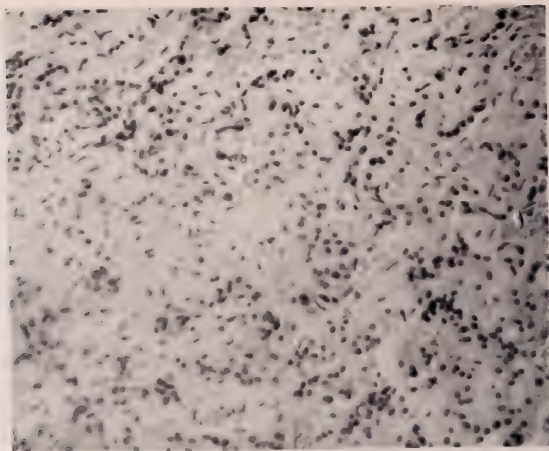


FIG. 17. Section of a pituitary showing loss of parenchyma and fibrosis in pituitary cachexia.



FIG. 18. Section of the tuber cinereum showing a focal luetic lesion (gumma) in a case of diabetes insipidus.

As he gained weight many purplish striae of the abdominal wall made their appearance. Shortly before his admission to the hospital, at the age of 26 years, his libido began to decline and in the course of a few weeks he became completely impotent.

*Examination.* The patient had obesity of the buffalo type, his eyes were porcine and his neck thick and short (fig. 20). The ocular fundi showed peripapillary edema, discrete areas of acute choroiditis and hypertensive vascular changes. The heart was enlarged, to the left. Numerous purplish striae were present over the abdomen. There was a cervico-dorsal kyphosis. The pelvis and prostate were small, the testes felt sclerotic. There were chronic ulcerations of the skin over the lower tibiae. Cutis marmorata was present. The blood pressure varied from 160 systolic and 110 diastolic to 180 systolic and 136 diastolic.

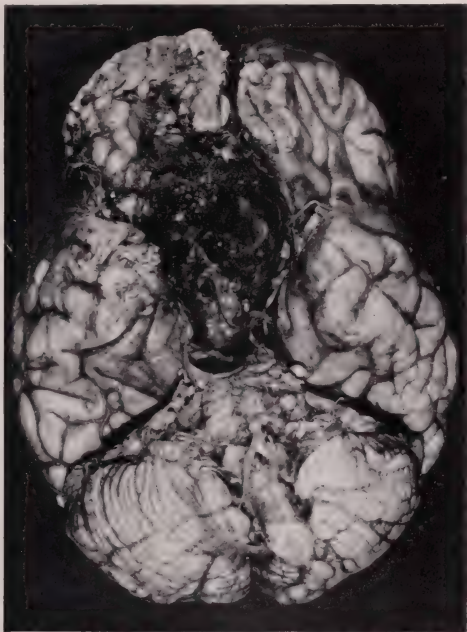


FIG. 19. Tumor destroying the hypothalamus in a case of Froehlich's syndrome.

*Laboratory data.* The red blood cells numbered 5.31 million per c.mm. The urine was normal. The blood urea was 17 mg. per 100 cc., the cholesterol 500 mg. per 100 cc. The fasting blood sugar was normal but glucose tolerance was decreased, the blood sugar level being 175 mg. per 100 cc. three hours after the ingestion of 50 grams of glucose. The basal metabolic rate was between -14 and -18 per cent. The urine contained no excess of female sex hormone; male sex hormone was not determined.

X-ray examination revealed vertebrae with the appearance of "*Fischwirbel*." There was extensive demineralization of the entire skeleton. The epiphyses of the tibiae and fibulae were ununited. The sella turcica was normal.

*Course.* Radiotherapy to the pituitary region yielded no improvement in the patient.

Despite failure to reveal evidence of an adrenal tumor by perirenal air insufflation exploration of the adrenals was considered advisable. Both adrenals were visualized at operation and appeared normal. Eight days post-operatively the patient developed a *Bacillus Welchii* infection of the wound and he died three days later.

*Post mortem examination.* There was evidence of Welch bacillus sepsis. The adrenals were normal in size, shape and position. The thymus gland was normal. The testes were



FIG. 20. Case of Cushing's syndrome

sclerotic. No changes in the endocrine glands could be found to account for the clinical syndrome.

The material available in this case consisted of several sections of the pituitary body hardened in formalin and embedded in paraffin. Hematoxylin and eosin stain and the Crooke modification of Mallory's acid-fuchsin, aniline-blue method were performed. *Pars anterior.* The fibrous tissue stroma throughout the lobe was not well marked, resulting in a lack of definition between the acini. The eosinophile, chromophobe and basophile



cells were evenly distributed, although a large collection of basophiles was present near the pars intermedia. The eosinophile cells were normal in appearance although strikingly reduced in number. The basophile cells showed well-marked hyalinized areas in the cytoplasm together with "vacuolization." The areas of hyalinization were extremely well marked. In one and the same cell one could see very distinctly the coarse, dark-blue granules surrounding somewhat punched-out areas which were pale blue in color and entirely free from granules. *Pars intermedia.* This area showed no change from the normal. *Pars posterior.* Near the center of this lobe there was an irregular collection of basophile cells. They were small, irregularly shaped and showed no tendency to arrange themselves into acini. The granules in the cytoplasm were fairly well marked. A few vacuoles were noted. No areas of hyalinization could be seen in this collection.

*Comment.* While the patient presented all of the features said to be typical of Cushing's syndrome the post mortem findings revealed no changes in the adrenals nor any alterations in the pituitary body which may be considered significant. It leaves open the question of the underlying pathophysiologic cause or causes of the syndrome.

#### SUMMARY

The hypothalamus is a central regulator of the autonomic nervous system, the pituitary an analogous regulator of endocrine function; pathologic obesity, sexual dystrophy, diuresis and certain other vegetative dysfunctions such as skeletal dwarfism and infantilism have been attributed to disturbances of function of one or the other. A review of recent progress in investigation of hypophysial and hypothalamic physiology, correlated with the authors' clinical data, reveals their interdependence, collaboration and duplication of function. Experimental and clinical studies indicate that hypothalamic disorders without hypophysial disease may yield obesity by increasing desire for food and decreasing activity, while with disturbance of the hypophysis selective deposition of fat may occur. Hypo- or hyperfunction of the pituitary may provoke hypo- or hyperthyroidism, respectively, and it seems likely that dysthyroidism may result from hypothalamic dysfunction. Over- or underdevelopment or involution of the sex organs is frequently a manifestation of disturbed hypophyso-hypothalamic function, resulting from disease of either one or both in combination. Similarly, growth and water balance are controlled by interdependent functioning of the two and disturbances may result from damage to either the neural or the endocrine center. Manifestations of hypoadrenocorticism accompany hypopituitarism but conversely there is evidence that hypothalamic disease may be a factor in hyperadrenocorticism; it therefore seems probable that the hypothalamus, the pituitary and the adrenals join action in some biological adaptations. The classical syndromes of gigantism and acromegaly result from acidophilic hyperpituitarism, the former in pre-, the latter in post-pubertal individuals. Hypopituitarism prepubertally results in dwarfism, after puberty in cachectic states (Simmonds' disease). Froehlich's syndrome, diabetes insipidus and some cases of Cushing's syndrome are the products of combined hypophyso-hypothalamic dysfunction. All of these states are dynamic processes which implicate the thyroid, the adrenals, the gonads and provoke widespread physiological and anatomical alterations.

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## THE USE OF SPLIT-THICKNESS SKIN GRAFTS IN THE CONSTRUCTION OF AN ARTIFICIAL VAGINA

MORRIS A. GOLDBERGER, M.D. AND JOSEPH A. GAINES, M.D.

(New York, N. Y.)

*From the Gynecological Service, The Mount Sinai Hospital*

A variety of operative procedures have been advocated during the past forty years for the construction of an artificial vagina. The trend toward simplicity and safety is epitomized in the non-operative technic suggested by Dr. Robert T. Frank (1) in 1938 for congenital absence of the vagina. By teaching the patient to apply daily pressure against the mucous membrane in the introital region, with tubes of increasing diameter, Dr. Frank was able to establish artificial canals, sufficient for sexual intercourse in 5 out of 6 cases. This procedure is heartily endorsed. It undoubtedly can be applied to young women with resilient perineal tissues who are intelligent and cooperative enough to persist with this therapy over a period of months, and who intend by marriage to maintain a functioning vagina. It would appear also to be especially applicable to incompletely developed vaginæ, and in those instances where operative intervention is refused. If, however, the perineal tissues are rigid or scarred by previous operations; if the temperament of the patient precludes the pertinacity required by the Frank method; if a vagina longer than  $2\frac{5}{8}$  inches is desired, a more direct and quicker operative approach may be indicated. Ideally, such a procedure should be easily performed, with a minimum of risks, complications, disfigurement, and hospitalization.

The Baldwin (2) operation, utilizing a segment of small intestine as an artificial vaginal cavity, and the Schubert (3) modification, in which rectum is transplanted forward, are complicated procedures. They are not only technically difficult, but have been associated with a high morbidity and mortality. Full thickness, pediculated skin flaps derived from the labia minora and adjacent thighs have been used by Graves (4) and others (5 and 6) to line a dissected cavity between bladder and rectum. Though a distinct improvement, disturbing features, such as mutilation of the vulva, and occasional necrosis of the distal ends of the flaps, with infection and contracture of the vaginal vault are sometimes evident. The Frank-Geist (7) operation employs tubed pedicle flaps derived from the inner thigh. This procedure requires long hospitalization and multiple plastic stages. It produces bulky flaps, and may cause considerable scarring of the thigh. The Wharton (8) technic of maintaining a vaginal channel by a suitable mold for a period of three months, until ingrowing epithelium from the vestibule completely covers the space, seems simple and encouraging. However, because of the slow process of epithelization, diligent after-care is required. The formation of scar tissue is inevitable, with the possibility of diminished elasticity and a tendency to contracture. To secure a long, adequate vagina and a minimum of scar tissue, the inlaying of a split-thickness skin graft,



molded over a vaginal form, was described by Kerschner and Wagner (9) in 1930. The results have been most encouraging as evidenced by the experiences of Barrows (10), McIndoe and Bannister (11), Counsellor (12), Wharton (13), Counsellor and Sluder (14), and Miller and others (15). It is with this procedure that our report is concerned.

#### CASE REPORT

*History.* M. W., a 17-year old, white, single girl, had been referred to the hospital because of primary amenorrhea. Menstrua, including lower abdominal discomfort and nausea, had been experienced at regular intervals of three and one half weeks since the age of thirteen. Two years ago, at another institution, the diagnosis of "imperforate hymen" was made, and an operation was performed. A "Y" shaped incision was made through the hymenal membrane by the electrocautery, but only a few drops of blood was obtained. The amenorrhea continued.

*Examination.* On admission, the patient was found to be a well developed, adolescent girl. The body contours were feminine in type, with female escutcheon and hair distribution, and normally-developed breasts. The external genitalia revealed small labia minora, a fair perineum, and a small, flattened vestibule, covered by a slightly scarred, imperforate mucous membrane. On rectal examination, with a metal catheter in the bladder, only a thin ridge of tissue could be palpated between the rectal and urethral walls. Within the pelvis, a small, uterine structure was felt. Although ovaries were not distinctly evident to the examining finger, good estrogenic stimulation was apparent by the normally developed secondary sex characteristics. Intravenous pyelogram showed no coincident congenital abnormalities of the genito-urinary system.

*Operation.* After a preliminary investigation had ruled out the bare possibility that a secondary closure of the previously-performed hymenotomy might be a causative factor in the patient's amenorrhea, she was prepared for operation. The vaginal molds utilized in this case were fashioned from light pinewood, in the form of an elongated radio tube. They were of varying size, 12-15 cm. in length, and 4-5 cm. in width. They were covered by two rubber condoms, tied about a screw-eye inserted into the proximal end of the vaginal stent. Sterilization was affected by soaking in a 1:1000 solution of Zephiran Chloride.

By means of a Pagett dermatome, two oblong, split-thickness skin grafts, approximately 14 thousandths of an inch thick, were taken from the anterior surface of the upper thighs. The first graft covered the dome and distal third of the vaginal mold. The second graft was applied in circular fashion about the remainder of the obturator. The edges were approximated by interrupted sutures of 0000 plain catgut to create a snugly and evenly covered mold (fig. 1).

Through a transverse incision of the vestibular mucous membrane, just above the posterior fourchette, a plane of cleavage was easily secured. By blunt dissection, a tubular cavity was created between the urethra and bladder anteriorly, and the rectum posteriorly. Very little bleeding was encountered. At a depth of approximately 8 cm., a soft, bulging surface was felt. Despite a sound in the bladder, and a finger in the rectum, it could not be ascertained with certainty whether this "vault" was bladder wall, rectal wall or *cul-de-sac*. To clear this question, before proceeding with further dissection, the following procedure was carried out: A small amount of methylene blue solution was instilled into the bladder, and an assistant's finger placed into the rectum. Using a 22-gauge needle and a 5 c.c. syringe, the vault was carefully aspirated in the midline. Since the needle did not approach the rectal wall, and aspirated 1 c.c. of serous fluid, rather than methylene blue solution, the vault was apparently *cul-de-sac* peritoneum. This was further separated from the rectum and a small incision made, sufficient for finger exploration of the pelvis. By this means, the rudimentary uterus could be felt posteriorly, as well as the presence of an ovary. The *cul-de-sac* was then closed by two layers of interrupted sutures of 00

chromic catgut. The vaginal cavity was found to be approximately 11 cm. in length and of sufficient width to admit  $2\frac{1}{2}$  fingers. The vaginal mold, covered by the split-thickness graft, was inserted into the dissected channel and maintained in position by long, narrow, rubber tubing, passing through the screw-eye of the obturator, and attached anteriorly and posteriorly to a circular bandage about the waist.

*Postoperative course.* On the first post-operative day, it was evident by the edema and discoloration of the urethral meatus, that the vaginal form was compressing the urethra against the symphysis pubis. To release this pressure by the tense constrictor vaginae, a small incision was made, (under local anesthesia) through the edge of the vulvo-vaginal ring at 5 and 7 o'clock. An indwelling rubber catheter of small calibre was then placed into the bladder. Had a suburethral groove been cut in the proximal portion of the mold, this complication may well have been avoided. Between the 4th and 11th post-operative day, a low-grade temperature was evident, but the patient was not too uncomfortable. The vaginal obturator was then removed, followed by a gush of retained purulent fluid, probably related to the partial necrosis of the anterior urethra. After irrigating the vaginal space, and a close inspection with vaginal spades, it was found that, despite the local infection, the vaginal cavity was almost completely covered by healthy-looking, firm, skin lining. Only an insignificant area in the right lateral wall was denuded. The patient was able to void spontaneously, without difficulty. She was given instructions concerning the maintenance of the vaginal cavity by means of pyrex glass obturators. The patient

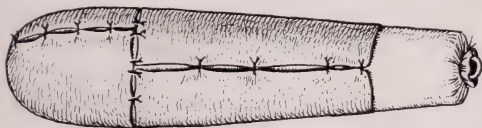


FIG. 1. The vaginal mold is covered by split-thickness skin grafts, 14 thousandths of an inch thick. Two oblong portions were used in the case described; one covering the dome and distal third of the vaginal form, and the other applied in circular fashion about the remainder of the intravaginal portion of the obturator. The edges are approximated by fine, interrupted sutures of 0000 plain catgut.

was kept in the hospital for four weeks, mainly because of our concern with the anterior urethra, but no functional damage had been done.

Examination 5 weeks after operation revealed a vagina 10 cm. in length and wide enough to admit 2 fingers. A slight circular constriction was felt about the level of the upper and middle third of the vagina. The epithelial lining of the cavity appeared soft and pliable. The patient was further cautioned concerning the necessity for maintaining the vaginal cavity by dilatation with properly fitting obturators.

#### COMMENT

The case reported indicates that an adequate artificial vagina can be established by a single operative procedure, which is not technically difficult, and does not entail undue hospitalization. That complications may occur must be conceded, but even these can be reduced to a minimum with experience, and attention to details.

Based on the previous experience of others, and our own observations, the following suggestions are made:

A preliminary intravenous pyelogram should be done, because of the high percentage of associated congenital abnormalities of the urinary tract, including

unilateral renal aplasia, ectopic pelvic left kidney, and duplication of the left ureter (14).

The mold employed should be light in weight, and wider at the distal end, not only to help retain it in the vagina, but also to compensate for greater contraction at the vault. The use of balsa wood, as suggested by Wharton (13), would be helpful since it is easily secured and fashioned into the required sizes. The necessity for a urethral groove, as proposed by Mahorner (16), to prevent compression of the urethra against the symphysis, is unequivocally acknowledged. The hollow lucite mold used by Counseller (14) is perforated at both ends for drainage, and thus of distinct aid in case of infection. In addition, the proximal  $1\frac{1}{2}$  inches is beveled superiorly and inferiorly where it lies under the urethra and over the anal pouch. To prevent perforation of the rectum by the stent, its proximal end should protrude slightly beyond the introitus.

To avoid subsequent irritation of the external urethral meatus, the initial transverse incision through the vestibular mucous membrane may be made immediately above the posterior fourchette; i.e., as far from the meatus as is feasible. The dissection of an adequate space is imperative (11 to 13 cm. in length and wide enough to admit 3 fingers). The cavity may be lengthened by pushing the *cul-de-sac* peritoneum forward, away from the rectum. A dePezzer or metal catheter in the bladder, and an assistant's finger in the rectum will often help differentiate bladder, peritoneum and rectal wall. The use of methylene blue solution in the bladder and aspiration, as utilized in the case reported above, may be of further aid. Bleeding should be well controlled, since the loss of graft is definitely related to hemostasis. If the bladder is inadvertently opened it may be carefully sutured and an indwelling catheter left in place. The operation may then be completed without further delay. If the vaginal outlet appears too snug, the constriction may be released by small incisions of the vulvo-vaginal ring at 5 and 7 o'clock.

The skin graft may be 12 to 15 thousandths of an inch in thickness. A single graft  $9 \times 2\frac{1}{2}$  inches should be adequate and may be taken from the upper, inner thighs or the abdomen. The prophylactic use of penicillin for a few days after operation may be helpful. Persistence in the maintenance of the canal until the contractile phase is over is of paramount importance. The mold should be worn most of the time for at least two months, and then as necessary.

#### SUMMARY

A case of congenital absence of the vagina is described, in which split-thickness skin grafts were utilized for the construction of an artificial vagina. Because a soft, pliable, and adequate cavity is achieved by this procedure, with a minimum of contracting scar tissue, it is recommended as the operation of choice when surgical intervention is indicated.

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## ANESTHESIA AS A CAUSE OF MATERNAL DEATH, WITH SPECIAL REFERENCE TO ASPIRATION ASPHYXIA AND ATELECTASIS

CHARLES A. GORDON, M.D., F.A.C.S.

(*Brooklyn, N. Y.*)

The real importance of anesthesia as a factor in maternal death is very difficult to discover. If anesthesia is mentioned on a certificate of puerperal death, it is not tabulated by the statistician, even though death is stated to have been due directly to anesthesia, even to aspiration asphyxia. Only from case records can the actual frequency of death from anesthesia be learned.

That thoughtless selection of the anesthetic for parturition complicated by toxemia, cardiac disease, tuberculosis and other respiratory infection may contribute to death is well known. And that anesthesia plays a significant role in death following prolonged labor and difficult operative procedures is equally obvious. But that anesthesia, in the absence of these complications, is fraught with danger is not so well appreciated.

In 1933, a committee of obstetricians (1), in an analysis of 2041 puerperal deaths in the City of New York from 1930 to 1932 found that death was due to anesthesia in 20 cases.

In 1937 Montgomery (2) studied 220 intrapartum deaths in Philadelphia, and reported that anesthesia was the primary cause of death in 5 cases, and a possible cause in 13 others.

The Committee on Maternal Welfare of the Massachusetts Medical Society (3) found that, of the 226 puerperal deaths recorded for the state in 1941, 10 were due to anesthesia; 6 of these deaths followed aspiration.

The Maternal Mortality Committee of the Minnesota State Medical Society (4) has reported that of 85 maternal deaths, the probable number for the state in 1943, 3 were due to anesthesia.

In Brooklyn, where, since 1937, every maternal death is reviewed by the Committee on Maternal Welfare of the Medical Society of the County of Kings we have been impressed by the frequency of death from anesthesia. In no case however, had the cause of death been assigned to anesthesia in the official vital statistics.

From 1937 to 1946 in a total number of 958 puerperal deaths, 43 were due to anesthesia. It has not been possible to weigh the seriousness of analgesia and amnesia, though evidence of their importance is impressive. In analyzing the maternal deaths due to anesthesia, they naturally fell into 3 groups, as due to (1) the toxic action of the anesthetic itself, and those due to (2) aspiration asphyxia and (3) atelectasis, whether from aspiration or otherwise. The nature of the anesthetic used, the type of delivery and the causes of death appear in Table I.



## DEATHS DUE TO THE ANESTHETIC ITSELF

In all 17 cases in which death is attributed to the toxic action of the anesthetic itself, death occurred on the delivery table. In 3 of these cases associated with operative pelvic delivery, data are insufficient to establish the cause of death more precisely than stated on the certificate of death as status lymphaticus (1 case) and anesthetic shock (3 cases). In 2 cases in which death occurred during administration of caudal anesthesia, the cause was said to be cardiac disease in one case and cerebral embolism in the other. Other cases of death under anesthesia but associated with eclampsia or hemorrhage are not included. Since this paper is concerned principally with aspiration asphyxia and atelectasis, tabulation of these 17 deaths will be sufficient (Table II).

TABLE I  
*Anesthesia as a cause of maternal death*  
43 cases

ANESTHETIC	TYPE OF DELIVERY					CAUSE OF DEATH			
	Spon- taneous	Forceps	Version	Ectopic	Cesar- ean section	Toxic	Aspira- tion	Atelec- tasis	Total
Ether.....	4	6			1	4	4	3	11
Nitrous oxide.....	1					1			1
Gas, oxygen ether.....	3	5			9	1	9	7	17
Chloroform & ether.....		1				1			1
Ether & spinal.....		1					1		1
Spinal.....			1	1	7	8		1	9
Local & cyclopropane.....					1			1	1
Caudal.....		2				2			2
Total.....	8	15	1	1	18	17	14	12	43

## DEATHS DUE TO ASPIRATION

In the total number of 43 puerperal deaths due to anesthesia, aspiration of vomitus is known to have occurred in 14 cases. Though danger of death from this cause is thoroughly appreciated by anesthetists, case reports are so few in number that it may be assumed that many who practice obstetrics are not sufficiently aware of this hazard. Hall (5), in 1940, reported 14 cases in obstetrical patients, and stated that "a careful search of all the medical literature had failed to yield a single detailed report." Guedel (6), however, in his text-book on anesthesia, had reported two obstetrical deaths due to aspiration asphyxia. Meurlin (7), in 1941, reported seven maternal deaths due to aspiration of vomitus. Abramson (8), in an excellent article reporting two cases, has recently reviewed the implications of anesthetic aspiration asphyxia. And, in 1946, Hartzell and Mininger (9) reported 20 cases of bronchopneumonia following ether anesthesia for delivery; in 9 of these cases vomiting was known to have occurred during or directly after anesthesia; none of these women died,

and in no case was there clinical evidence of serious illness. I have found no other case reports.

In 26 cases death was due either to aspiration asphyxia or atelectasis. Death from aspiration need not be prompt, and deaths attributed to atelectasis may be preceded by symptoms of suffocation. In either case the dramatic circumstances of death teach so valuable a lesson that all these cases are reported. Quotations are from the case summaries submitted to the Committee on Maternal Welfare. Non-essential obstetrical data are omitted.

Following aspiration of vomitus, death was instantaneous or nearly so, in 7 cases, and in 7 other cases aspiration is known to have occurred. The type of delivery, the anesthetic and the time relationship of anesthesia to the ingestion of food are shown in Table III.

TABLE II  
*Maternal deaths due to toxic action of the anesthetic*

ANESTHETIC	SPONTANEOUS	FORCEPS VERSION	ECTOPIC	CESAREAN SECTION	TOTAL	CAUSE OF DEATH
Spinal		1	1	6	8	respiratory paralysis anesthetic shock (3)
Ether	1	3			4	status lymphaticus (1)
Gas, oxygen ether				1	1	convulsions
Nitrous oxide	1				1	ventricular fibrillation
Chloroform & ether		1			1	degeneration of liver
Caudal		2			2	unknown
Total.....	2	6	1	1	7	17

#### NORMAL DELIVERY

*Case 1.* Age 23 years, para I, was admitted to the hospital shortly after dinner. One hour later, with the vertex crowning, vomiting occurred under gas, oxygen ether sequence, so the inhaler was removed. When anesthesia was resumed, she vomited again, became deeply cyanosed and died. The total time of anesthesia was four minutes. Artificial respiration and postural drainage were of no avail. After death, a live baby was delivered by low forceps. At necropsy the trachea and large bronchi were found filled with food.

*Case 2.* Age 33 years, para 0, was delivered spontaneously under light open ether given with uterine contractions. When anesthesia was resumed for episiotomy repair she "struggled furiously, tried to vomit and suddenly stopped breathing with face and extremities deeply cyanosed." Respiration was reestablished with the E&J resuscitator. Fifteen minutes later cyanosis deepened, bloody froth appeared on her lips and death ensued.

*Case 3.* Age 31 years, para 0, admitted to the hospital in active labor was given pentobarbital gr. VI and scopolamine gr.  $\frac{1}{160}$ . One hour later with vertex crowning, ether was administered. During induction she vomited large amounts of undigested food, became cyanosed and stopped breathing. Artificial respiration failed. At necropsy the bronchi were found almost entirely obstructed by food. The lungs showed edema, pleural petechiae and muco-purulent exudate in the bronchioles.

*Case 4.* Age 20, para O, colored. One hour after admission to the hospital, spontaneous delivery occurred under gas, oxygen ether sequence. "Immediately afterward she vomited a large amount of liquid and undigested food; this continued for several minutes, but at no time was there any sign of respiratory distress." Her blood pressure was 118 systolic, 80 diastolic and the pulse rate 100. She was slightly cyanosed as dyspnea and restlessness increased, and breathing became noisy. Death occurred shortly after the bronchoscopist removed a small quantity of fluid from the bronchi. At necropsy, edema was found; the trachea and main bronchi were congested but clear, and many of the larger bronchi were filled with purulent exudate. The upper and especially the lower lobes of both lungs showed consolidation.

#### INSTRUMENTAL DELIVERY

*Case 5.* Age 40 years, para IV. After two days in the hospital she was fully dilated. Under open drop ether anesthesia, forceps were applied. "After two attempts at traction, she vomited, aspirated and stopped breathing. Intratracheal intubation, suction and artificial respiration were futile."

TABLE III

*Maternal deaths due to asphyxia and atelectasis; known aspiration of vomitus*

DELIVERY	ANESTHETIC	TIME RELATION OF ANESTHESIA TO	
		Death	Food
Spontaneous	gas, oxygen ether	instantaneous	9 hours
		instantaneous	2 hours
Instrumental	ether	instantaneous	2 hours
		instantaneous	unknown
	gas, oxygen ether	instantaneous	unknown
		20 minutes	unknown
		12 hours	8 hours
Cesarean section	ether and spinal	next day	9 hours
		24 hours	unknown
	gas, oxygen ether	1 hour, 40 minutes	12 hours
		12 hours	12 hours
		48 hours	unknown
		74 days	unknown
	ether	75 hours	1 hour

*Case 6.* Age 29 years, para O. She had nothing by mouth for nine hours before delivery. During the first stage of labor, a period of nine hours, she was given morphin sulfate gr.  $\frac{1}{2}$  and scopolamine gr.  $\frac{1}{300}$ . After three hours in the second stage she showed a good crown and gas, oxygen ether anesthesia was begun. "From the start she choked and coughed considerably, so the anesthetic was changed to open drop ether. With some difficulty she was put under for application of forceps. She vomited a small amount of green liquid and coughed up some bloody mucus." Delivery was simple. Shortly afterward, her color was poor, the pulse rapid, coughing continued and she had a severe chill. Pulmonary edema and atelectasis were shown by x-ray. She continued to raise bloody sputum until death in an oxygen tent on the second day. Treatment included intravenous hypertonic glucose and phlebotomy.

*Case 7.* Age 37 years, para I, had manual rotation of the occiput under ether anesthesia. Recovery was complicated by vomiting and aspiration. Signs of asphyxia and atelectasis were present before delivery was effected by forceps under spinal anesthesia. Death 24 hours later.

*Case 8.* Age 28 years, para O, after long labor was delivered by midforceps and Dührsen's incisions. She had nothing by mouth for eight hours preceding delivery. During induction of anesthesia under gas, oxygen ether sequence, she coughed and vomited blood stained fluid. Breathing ceased for one minute, and she became deeply cyanosed. Delivery was accomplished under open drop ether, with respirations 52, and blood pressure 90 systolic and 60 diastolic. Cyanosis and cough became worse, respiration more labored and the pulse rate increased to 160. Resonance was impaired and bronchial breathing appeared in the lower lobe of each lung. Death occurred in 12 hours.

*Case 9.* Age 22, para O, colored, after 43 hours of labor was delivered by forceps under gas, oxygen ether sequence. "During anesthesia, she vomited, aspirated, coughed and had slight nasal bleeding." A suction tube was used. Respirations were grunting, and frank bloody and bloody froth came from her nose and mouth. The pulse rate rose to 160, and blood pressure fell. Pulmonary edema rapidly appeared and she died in 20 minutes.

#### CESAREAN SECTION

*Case 10.* Age 29 years, para I. Cesarean section under gas, oxygen ether anesthesia after 13 hours of labor. During closure of the abdominal wall, she vomited large amounts of food, though she had no food during the 12 hours she was in the hospital. A considerable number of food particles were quickly removed from the larynx, but not before death. At necropsy, no food was found in the bronchial tree.

*Case 11.* Age 22 years, para O, weighing over 300 lbs. After 12 hours of labor, cesarean section was performed under gas, oxygen ether sequence. "She took a very poor anesthetic, with frequent attempts to vomit." Immediately afterward, respirations increased to 80, breathing was labored and the pulse rate rose to 170. Death occurred 48 hours later, temperature rising to 107°F.

*Case 12.* Age 30 years, para O. History of myomectomy. Shortly after dinner at home, she suffered sharp abdominal pain, and was in the operating room one hour later for rupture of the uterus. She took a very poor anesthetic (ether), vomiting frequently and requiring one-half hour for induction. A live baby was removed from the uterus, and the rent was closed. She was given 500 c.c.'s of blood, since she was in shock. Breathing was labored, and rales were widely present over both lung fields. The next morning the temperature was 103°F., and respirations were 36. On the following day bilateral bronchopneumonia and general pulmonary edema were present. Treatment included oxygen, blood transfusion, hypertonic glucose and sulfapyridine. Death occurred 75 hours after operation.

*Case 13.* Age 27 years, para O, with primary thrombocytopenic purpura had cesarean hysterectomy under gas, oxygen ether sequence. Just prior to the planned splenectomy, she "vomited considerable brownish red material and aspirated," and her blood pressure fell from 108 systolic and 42 diastolic to 70 systolic and 40 diastolic. She was placed in Trendelenburg position, and transfusion was begun. While waiting for the anesthetist to regain control of the patient, pulse and blood pressure improved somewhat, and splenectomy was then performed. She was returned to bed with cold, clammy cyanotic skin, rapid labored respiration and blood pressure 70 systolic and 40 diastolic. Bloody frothy liquid poured from her mouth and nose. Treatment included catheter aspiration and high Trendelenburg position until death occurred one and one-half hours later. Necropsy showed aspiration pneumonitis.

*Case 14.* Age 27 years, para O. After 102 hours of labor, which included failed forceps, cesarean hysterectomy was performed under ether anesthesia. She took the anesthetic poorly, vomiting. Immediately after operation, the pulse rate rose to 160 and cyanosis was noted. The puerperium was highly febrile, with chest pain and frequent cough. Three blood transfusions were administered before the 34th day, when she coughed up foul sputum. Repeated roentgenograms showed abscesses in the upper lobe of the right lung. Eleven sputum examinations were negative for tubercle bacilli, showing hemolytic and green

streptococci. Death occurred on the 37th day postpartum during bronchoscopic irrigation of a large abscess cavity.

#### DISCUSSION

The obstetric delivery, operative or otherwise, is not comparable with the planned surgery of the operating room. The second stage of anesthesia is bristling with hazards, and not only because administration of the anesthetic is commonly assigned to the ill trained and inept. In many of the cases reported here anesthesia was carried out by a well trained anesthetist. If induction is not smooth, the entire period of anesthesia may be stormy. Selfcontrol is abolished in this stage, and women who have repressed their fears and emotions throughout labor are apt to thrash about and resist induction. In fact outward calm is often ominous. More than fear of delivery itself, anxiety for the baby may so increase reflex excitability as to make induction troublesome and perhaps impossible, especially with nitrous oxide.

The physical and emotional stress of labor retards gastric peristalsis, so that food may remain in the stomach for a long period of time, often longer than twelve hours. If labor is unduly prolonged, the peristaltic activity of the entire intestinal tract is slowed, and both small and large bowel become distended. With the onset of active labor, gastric activity stops. Attempts at vomiting become more serious if the stomach is not empty.

The patient may find herself suddenly prepared for delivery, shortly after dinner. Varying depth of anesthesia while awaiting arrival of the obstetrician may result in accidental rise of the anesthetic level to the vomiting area. Or this same misfortune may befall the experienced anesthetist during cesarean section when the patient has been carried lightly because depth is not necessary, and protection of the baby from high concentration of the anesthetic is desirable.

Vomiting occurs late in the second stage of anesthesia either just before induction is complete, or at the beginning of recovery. Reflex activity of the vomiting center is due to significant delay at this point. Holding the breath and reflex swallowing may presage vomiting. A period of apnea or retching is particularly dangerous, as it is often associated with hard tonus of the masseter muscles, and a deep inhalation with aspiration and high concentration of the anesthetic in the blood. Sedative drugs may contribute to the danger of aspiration by depression of the cough reflex, and may arrest respiration during the period of induction if they have been given in large doses.

#### DEATHS DUE TO ATELECTASIS

Maternal death may be due to atelectasis even if no anesthetic has been administered. The following case, which is not included in the 43 cases of maternal death due to anesthesia is reported in support of this statement.

*Case report.* Age 39 years, para VIII, was delivered spontaneously without anesthesia, after 36 hours of labor. She coughed considerably during the first stage of labor, and a few moist rales were heard in the upper lobe of the left lung. On the third day postpartum she became orthopneic, and atelectasis of the upper lobe of the left lung was diagnosed clinically



and by x-ray. A thick bloody mucous plug was removed through a tracheal catheter, and bronchial casts were coughed up. Oxygen and penicillin were administered. Shortly afterward, large mucous plugs were removed from the right and left main bronchi through a bronchoscope, and improvement followed. Respiratory embarrassment increased with cyanosis and cough, and she died 33 hours postpartum.

There were 12 deaths due to atelectasis after administration of anesthesia. Aspiration may have occurred in some of these cases, and probably did, but it was not reported. In 2 cases induction was troublesome, and in 4 others recovery was complicated. Vomiting and aspiration may pass unnoticed if a closed system of administration of anesthesia is used. These cases are reported briefly with omission of clinical data not pertinent. Summary will be found in Table IV.

TABLE IV  
*Maternal deaths due to anesthesia atelectasis*

DELIVERY	ANESTHETIC	HOURS IN LABOR	TIME RELATION OF ANESTHESIA	
			first symptoms	to death
Spontaneous	ether	unknown	12 hours	28 hours
Instrumental	gas, oxygen ether	7	24 hours	3 days
		27	immediate	4 days
	ether	32	$\frac{1}{2}$ hour	10 days
		70	immediate	5 hours
		31	1 hour	4 days
Cesarean section	gas, oxygen ether	None	immediate	4 hours
		None	immediate	5 hours
		8	immediate	5 hours
		None	immediate	1 hour
	spinal	30	8 hours	14 hours
	local & cyclopropane	None	3 hours	5 days

#### NORMAL DELIVERY

*Case 1.* Age 27 years, para 0, was delivered of an assisted breech under ether anesthesia. Deep cyanosis and labored breathing appeared twelve hours later. Oxygen was administered and she improved greatly, but twelve hours later dyspnea recurred, cyanosis deepened and death ensued four hours later.

*Case 2.* Age 37 years, para IV. After seven hours of labor, "spontaneous delivery occurred under light gas oxygen ether anesthesia with her pains." Twenty-four hours later bronchial breathing was noted in the lower lobe of the left lung, and moist rales were found in the lower lobe of the right lung. Her abdomen was distended. Cyanosis deepened hourly, and unproductive cough was very troublesome. Death occurred on the third day, with consolidation of both lung bases, and the upper lobe of the left lung.

#### INSTRUMENTAL DELIVERY

*Case 3.* Age 35, para 0. Manual rotation and forceps delivery after 27 hours of labor. Gas, oxygen ether anesthesia lasted one hour. Coming out of anesthesia, she showed signs of respiratory embarrassment, became cyanotic and coughed frequently. The respiratory rate rose to 40 at times, and the pulse rate was 120. The next day she coughed frequently, mild cyanosis persisted, and signs of pneumonia were present in the lower

right chest and left interscapular area. Cyanosis deepened and bilateral lung involvement was apparent. Death on the 4th day.

*Case 4.* Age 32, para 0, was delivered by low forceps under gas oxygen ether anesthesia, after 32 hours of labor. One-half hour later she was cyanosed, with gasping inspiratory dyspnea, tachycardia and a weak thready pulse. The next day breathing was stertorous, and her cough paroxysmal and dry. Disseminated bronchopneumonia was shown by x-ray. Course was septic for 10 days, with increasing dyspnea and severe substernal pain.

*Case 5.* Age 27, para I, colored. After 70 hours of labor a large stillborn child was delivered under ether anesthesia by a difficult forceps operation and cleidotomy. "While reacting from anesthesia she began to gasp for breath and became cyanosed." Shortly afterward her pulse rate was 140 and her temperature 104°F. Pulmonary edema increased, and respiration became more labored. Treatment included oxygen, atropin and cardiac stimulants. Death 5 hours postpartum.

#### CESAREAN SECTION

*Case 6.* Age 40 years, para II. After labor of 31 hours in which scopolamin gr.  $\frac{1}{150}$  and nembutal grs. 3 were administered, a frank breech was delivered under open drop ether anesthesia which lasted twenty minutes. No vomiting or other untoward symptoms were observed. One hour later dyspnea occurred, without chest pain. Respiratory rate rose to 36, and the pulse to 120. Cyanosis appeared. Breath sounds were absent in the entire lower lobe of the right lung, and gray-yellow sputum, which later became bloody, was expectorated. The pulse rate rose to 140, becoming irregular and thready. Respiration became more labored and edema increased until death occurred 15 hours postpartum. Treatment included morphin, atropin and oxygen by face mask.

*Case 7.* Age 26, para IV, colored. Cesarean section under gas, oxygen ether anesthesia. The operating time was one hour. "As the patient was removed to the stretcher, she suddenly became pale, her pulse failed and the systolic blood pressure was unobtainable." She was thought to be in shock. Dyspnea steadily increased until she died five hours after operation. Treatment included plasma and stimulants. Necropsy showed massive atelectasis involving the lower lobes of right and left lungs, nearly all of the upper lobe of the left lung and two-thirds of the upper lobe of the right lung. At necropsy the smaller bronchioles were filled with watery material, but no mucous plugs were seen; general pulmonary edema was present.

*Case 8.* Age 45 yrs., para II. After 8 hours of labor, cesarean section and myomectomy were performed under gas, oxygen ether anesthesia. Induction was difficult requiring one-half hour, the anesthetist stopping three times "to remove a mucous plug," as cyanosis recurred frequently. After operation she appeared to be in shock and was given blood and plasma, though blood loss had been minimal. Death occurred five hours later.

*Case 9.* Age 25, para I. Cesarean section under gas, oxygen ether anesthesia. The patient stopped breathing three times during the operation, which lasted 30 minutes. On one of these occasions artificial respiration was continued for several minutes. There had been no undue hemorrhage, yet she appeared to be in shock. The pulse rate rose to 144, cyanosis increased and death occurred one hour later. Treatment included glucose and stimulants.

*Case 10.* Age 32 years, para III. Lower segment cesarean section was performed under spinal anesthesia after 30 hours of labor. Heart and lungs were negative. Eight hours after operation cyanosis, and harsh unproductive cough appeared and respiratory distress steadily increased. Rales were heard all over both lung fields. Death occurred 14 hours after operation.

*Case 11.* Age 37, para VII, colored. Cesarean section under gas, oxygen ether anesthesia for placenta previa. "She coughed for three hours afterward, and seemed to have a lot of mucus in her throat." Blood pressure fell to 70 systolic and 50 diastolic and breathing was labored, and finally Cheyne-Stokes. There was no hemorrhage. Death four hours after operation.

*Case 12.* Age 30 years, para I, cardiac, was delivered by cesarean section after three weeks in bed in the hospital. Morphine gr.  $\frac{1}{2}$  and nembutal gr.  $4\frac{1}{2}$  preceded procaine block and infiltration anesthesia. Cyclopropane was administered when the peritoneum had been opened. A few hours later coughing, cyanosis and slight fever appeared, and signs of pneumonitis were found, on the following day, in the lower lobe of the right lung. Death on the fifth day post-partum.

#### DISCUSSION

Atelectasis, which implies at least partial collapse of the alveoli, follows bronchial obstruction or decreased ventilation of the lung field and poor endobronchial drainage. Bronchial ciliary action is ineffective in the presence of masses of secretion or vomitus. Mucus is aspirated more frequently than vomitus, and more often without the knowledge of the anesthetist, but aspiration is not essential. Failure of expansion of the lung may be due to reduced respiratory depth or force, the result of compression and inactivity of the chest. The voluntary splinting of the diaphragm and scant pulmonary excursions associated with severe pains of labor may result in decreased bronchial respiratory movements and drainage block of the alveoli. Excessive bronchial secretion and sedation contribute to the danger of atelectasis. Goodman and Gilman (10) state that morphine, even in small doses, is a continuous depressant of respiration, and the cough reflex, which is finally abolished if large doses have been used. Barbiturates in large doses also depress the medullary respiratory center.

Cassels and Rapoport (11) who have very clearly discussed the signs of atelectasis say that the most important single sign is asymmetric movement of the chest. They believe that shift of the mediastinum to the affected side with compensatory shift of the heart borders and apex beat, may account for the rapid pulse and the fall in blood pressure by interference with the flow of blood through the great vessels. Percussion and auscultation may not be relied upon for early diagnosis. Changes in density of the lung will be shown by x-ray as atelectasis increases. Abdominal distention is frequently noted. Bloody froth from the mouth or nose, and paroxysmal coughing and choking are commonly observed. Breathing becomes difficult, labored and often stertorous, and pulse and respiration quicken. Shock may be profound. Temperature may be elevated early. And pulmonary edema may be an early symptom too. Cyanosis is consistently present.

Stomach contents may enter the lungs in considerable amount, yet evidence of aspiration may not be found at autopsy. Irons and Apfelbach (12), however, in an excellent and noteworthy paper, point out the importance of necropsy performed within an hour or two of death, so that postmortem changes do not confuse the issue; the frequency of aspiration of stomach contents may be proved by characteristic tissue alterations and cultures of lung tissue, tracheal and stomach contents and the blood.

#### RECOMMENDATIONS

No food liquid or solid, should be given during labor, if birth may be anticipated within twelve hours. If delivery should impend within a period of twelve

hours after admission to the hospital, it should be assumed that the stomach is not empty, and vomiting should be induced if general anesthesia will be administered for delivery. Gastric lavage is seldom feasible, and not so effective.

There is considerable risk in allowing food to any woman in labor once a pattern of regular uterine contractions is established. Intravenous administration of glucose, salt and finally amino acids or plasma will suffice. It is conceded that desultory or very long labor presents a food problem which requires good judgment of the obstetrician.

It is clear that the anesthetist should be sufficiently trained to be acutely aware of the hazards of induction of anesthesia and emergence. Apparatus for suction should be in readiness. The head end of the delivery table should be lower than the foot, or the patient's head, at least, should be lowered through a horizontal to a declined plane. If the character of the respiration is satisfactory, the patient should be carried through the stage of induction as rapidly as possible. If the breath is held, or if attempts at vomiting occur, anesthesia should be stopped at once, and the patient's head promptly turned to one side. Anesthesia should never be crowded at this point. When induction is complete great care should be exercised to see that the anesthetic level is not lowered until the operative procedure is at an end. Recovery, and a second anesthesia for the repair of episiotomy is another invitation to danger.

Recovery from ether anesthesia is slow, and the excitement of emergence may be high in those women in whom it has been difficult to induce anesthesia. The hyperpnea induced by carbon dioxide will hasten recovery and increase the safety of this stage of anesthesia. The recovery bed should be elevated at its foot, and the patient placed in it on her side. She should be closely watched, and deep breathing or coughing may be encouraged until she is mentally alert. Bronchoscopy may be indicated.

Local anesthesia is much safer than general. Episiotomy and low forceps delivery can be easily and satisfactorily accomplished under local infiltration. And pudendal block, in the hands of the expert, is satisfactory for delivery from midpelvis. Dutch midwifery (13) deprecates entirely the employment of general anesthesia in normal cases. I hold no brief for this practice, though it does add to the safety of parturition, and it is a fact that local anesthesia will not be found suitable for every woman, or by every practitioner of obstetrics.

If nitrous oxide is mixed with twenty volumes per cent of oxygen, its margin of safety is great. Prior use of sedatives during labor will increase the depth of anesthesia. Combined with local anesthesia, nitrous oxide is highly satisfactory. It may be difficult, however, even impossible, to anesthetize highly nervous women without anoxemia. In that event the gas, oxygen ether sequence is satisfactory and safe if administered by an alert trained anesthetist.

Spinal anesthesia has definite advantages for abdominal delivery, but its safety is uncertain and not comparable with local anesthesia. It is most dangerous in the hands of the obstetrician who uses it infrequently.

The speed of induction and recovery may appear to make cyclopropane an asset to the obstetrician, but its potency, the danger of ventricular fibrillation

and the hazard of explosion should prohibit its use. Though it is possible to administer a high percentage of oxygen with cyclopropane, Beecher (14) has pointed out that a much higher percentage of oxygen is possible under full surgical anesthesia under ether. He states too that "a considerable change of attitude of surgeons toward cyclopropane has become apparent. The early enthusiastic approval of many has in some cases given way to questionings and doubt."

#### SUMMARY

1. Forty-three puerperal deaths from anesthesia are reported with brief clinical data in 26 cases of aspiration asphyxia and atelectasis.

2. The controllable factors of death from these causes are discussed, and attention is directed to the importance of anesthesia in parturition.

3. Suggestions for prevention of puerperal death from aspiration asphyxia and atelectasis are presented.

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## SYMPATHECTOMY FOR THE RELIEF OF PELVIC PAIN IN WOMEN

J. P. GREENHILL, M.D.

[Chicago, Illinois]

Pain in the female pelvis may be divided into many types but for the purposes of this paper the division will be made into two groups. The first is that in which the cause of the pain can be removed by surgical means. The second is the group in which the source of the pain cannot be eliminated readily either because the seat of its origin is unknown or it involves structures so vital that surgery cannot be employed. The first group may be further divided into subgroups: pain which is sudden or acute and distress which is chronic. In the first subgroup is included the pain arising from ruptured ectopic pregnancy or corpus luteum cyst and torsion of an ovarian cyst. In the second subgroup is the pain due to pelvic inflammatory disease, endometriosis and pelvic neoplasms. Both the acute and chronic pain in the first group can be relieved by surgically removing its cause.

In this paper I should like to discuss only that type of pelvic pain the origin of which is either unknown or if known its cause cannot or should not be removed surgically. In this category I include the following types of pain: (1) severe dysmenorrhea, (2) endometriosis in young women, (3) inoperable carcinoma of the female genitals and (4) pelvic pain of unknown origin unsuccessfully treated by one or more laparotomies.

Because the site of the foregoing types of pain cannot be removed, some other method of relieving the pain must be employed in these cases. Drugs, chiefly the analgesics and opium derivatives, are generally given but they are unsatisfactory because they relieve pain for only a few hours at a time. Endocrinotherapy, physiotherapy and even roentgenotherapy are likewise of little or no help. A method of treatment which is highly successful in all of these cases is removal of the pelvic sympathetic plexus. This operation is known under a variety of names such as pelvic sympathectomy, pelvic neurectomy, resection of the presacral nerve and resection of the superior hypogastric plexus. The operation is relatively simple and may be performed by anyone trained to do abdominal surgery.

Before describing the anatomy and technic of pelvic sympathectomy I should like to discuss the four major indications for the operation.

*Severe dysmenorrhea.* Dysmenorrhea is generally divided into primary and secondary types. The secondary type is associated with a pathologic disturbance in the pelvis such as endometriosis, uterine fibromyomas, inflammatory disease or stenosis of the cervix from injudicious cauterization or other causes. The menstrual pain can be relieved by surgically removing the pathologic condition. On the other hand primary dysmenorrhea is not associated with any detectable abnormality in the pelvic organs and because of this its treatment is most unsatisfactory. There is no unanimity of opinion concerning

the cause of severe primary dysmenorrhea. Undoubtedly there is more than one etiologic factor. Since the cause of the pain is unknown the treatment is empiric. Chief reliance is placed on analgesic drugs, atropine sulfate and the endocrines. None of these are uniformly successful and thus after medication fails, physical means, such as dilation of the cervix, with or without curettage and with or without the insertion of a stem pessary into the cervical canal, are usually employed. These procedures also are unsatisfactory because when they are effective the benefit is nearly always temporary. On the other hand pelvic sympathectomy is almost permanently 100 per cent successful in severe dysmenorrhea (1). However, no girl or woman should be subjected to pelvic sympathectomy until all conservative measures have been tried over a sufficiently long period of time. In most instances of primary dysmenorrhea there is a large psychic factor and this must be considered while the conservative measures are being used.

*Endometriosis in young women.* It is well known that endometriosis produces pain as long as estrogen stimulations exist. Therefore the simple way to relieve such pain is to remove both ovaries or destroy ovarian activity by radiation therapy. This treatment is proper in women more than 40 years of age but not in young women. In the latter every effort should be made to conserve normal ovarian tissue, preferably by retaining an intact healthy ovary if one is present. If both ovaries are endometriotic as much healthy ovarian tissue as possible should be preserved. Following such conservative operations many women remain well without any further treatment. Others, however, continue to have periodic pain just before and during the menstrual periods. Because of this I believe that whenever a conservative operation is performed for endometriosis a pelvic sympathectomy should be done at the same time. This operation requires only a few more minutes of time and will prevent most of the pain which would otherwise be present after a conservative operation. Not only will the pain be relieved in most of the cases, but it seems that pelvic sympathectomy benefits the endometriosis itself. This may be due to the vasodilation that follows sympathectomy.

*Carcinoma of the uterus.* Carcinoma of the uterine cervix is one of the most serious afflictions that can develop in a woman because at least three out of every four women so afflicted die from it as do about half of the women with cancer of the body of the uterus. Furthermore, nearly all such women suffer excruciating pain during the latter part of their lives and in a large proportion of them the almost unbearable pain is constantly present. This is due to the fact that the sensory nerves become involved in the malignant growth. There are at present three means of relieving this type of pain. The first and the one used almost exclusively at present is the administration of derivatives of opium, chiefly morphine. However there are disadvantages to this form of therapy, particularly the necessity of giving constantly increasing doses as the patient's tolerance increases, the nausea and vomiting which some women experience, the idiosyncrasy of others, the addiction that develops in many women, the excitement produced in some and the expense for poor patients. The second method of giving relief from pain is surgical and consists essentially of pelvic sympathectomy

(2) and cordotomy. The latter operation will definitely relieve pelvic pain but it should be performed only by one skilled in neurosurgery. The operation requires a laminectomy of the spines of the second, third, fourth and fifth thoracic vertebrae and "unless the incision in the cord is accurately placed, the pain may not be completely relieved as the motor pathways may be damaged, resulting in paralysis of the legs and interference with sphincter control" (3). The third means of relief consists of blocking the nerves which conduct pain sensations. For carcinoma of the pelvic organs one of the most effective procedures is intraspinal (subarachnoid) injection of alcohol. I have employed intraspinal alcohol injections in many cases of cancer with excellent results (4).

Pelvic sympathectomy should be done at the time of a Wertheim operation as it requires only a few extra minutes to perform and the consequent benefits to the patient, should there be a recurrence, are manifold. Likewise in all cases when an abdominal operation is performed for carcinoma of the body of the uterus, tubes or ovaries, a pelvic sympathectomy should be performed prophylactically to prevent pain in the event of recurrences. De Sousa Pereira (5) maintains that when abdominopelvic sympathectomy is performed in cases of cancer of the cervix the results of radiation therapy after such an operation are better than if the sympathectomy had not been performed. He attributes this improvement to the increased blood supply caused by vasodilatation following this procedure. In extensive cancer of the genitals for which a laparotomy is not performed, the severe pain can be relieved much more simply, economically and safely by intraspinal injection of alcohol than by pelvic sympathectomy.

*Pelvic pain of unknown origin.* Occasionally women are seen who complain of more or less constant pain, who were subjected to one or more laparotomies without relief and who are called hypochondriacs or neurotics. Most of these women first have their appendix removed, then they are subjected to one or more subsequent laparotomies for ovarian cysts, adhesions and other causes and still their pain persists. In such women a pelvic sympathectomy, even if the source of their pain cannot be ascertained, will result in dramatic relief.

#### TOPOGRAPHIC ANATOMY OF PELVIC SYMPATHECTOMY

The presacral plexus can be found readily if one looks for a triangle the base of which corresponds to a line uniting the two common iliac arteries at the level of the sacral promontory; the sides of the triangle are these arteries and the apex is the point of bifurcation of the aorta. This triangle occupies the lower third of the fourth lumbar vertebra, the last intervertebral cartilaginous disk and the fifth lumbar vertebra. The base of the triangle is about 7 cm. in length and the distance from the base to the apex is almost 6 cm. A large part of the left side of the triangle is occupied by the left common iliac vein, which arises from the inferior vena cava and passes downward from beneath the right common iliac artery to accompany the left common iliac artery. The triangle is divided vertically into two equal halves by the middle sacral artery, which arises from the back part of the aorta just at its bifurcation and courses straight down to the upper part of the coccyx. Since this vessel is felt easily through the peritoneum

it is often mistaken for the presacral nerve, which lies parallel to it. From the origin of the inferior mesenteric artery down to the bifurcation of the aorta, the nerve fibers lie on the aorta and are separated from it only by a layer of thin connective tissue. The branches of the plexus, which accompany the left common iliac vein, are separated from this vessel by areolar tissue, making elevation of the nerve easy. However, as the nerve fibers penetrate still farther down, they lie on the peritoneum and perichondrium of the last lumbar vertebra, and the cartilaginous disk between this vertebra and the sacrum. At this point the plexus lies above the middle sacral artery and veins.

The entire triangle is covered with peritoneum; hence the nerve plexus lies between the peritoneum and the underlying bones. The fibers are separated from the peritoneum by fatty tissue; the adiposity of this tissue depends on the obesity of the patient.

Usually the inferior mesenteric vessels may be seen to the left of the midline, but sometimes they are in intimate contact with the presacral nerve. This is due to an abnormal anatomic position and to the undue length of the pelvic mesocolon, whereby its right root is inserted in the midline or still farther to the right. Therefore in these cases the incision in the posterior parietal peritoneum must be made to the right of the midline and the nerve can be reached only through the thick mass at the base of the mesocolon. This is a difficult procedure.

In Elaut's (6) fifty dissections he never found the presacral nerve in front of the sacrum, but always above the promontory in front of the body of the fifth lumbar vertebra and the intervertebral cartilaginous disks below and above this vertebra. Thus the nerve was always prelumbar. Elaut found that the bifurcation of the nerve varied considerably. Usually it was at a point below the bifurcation of the aorta; occasionally it was at the same level as the division of the aorta, but rarely was it at the base of the triangle.

There is seldom any need to worry about the ureters except in those cases in which the pelvic mesocolon must be pulled to the left to permit exposure of the triangle. Only the right ureter must be considered, but since it adheres firmly to the peritoneum and the presacral nerve does not, it is easy to differentiate between the ureter and the nerve.

#### PHYSIOLOGY

Properly, two questions may be raised. One is whether the fibers of the sympathetic system are really sensory. Ranson (7) says that proof of this was offered by Edgeworth and that he confirmed Edgeworth's observations. If the roots of the spinal nerves are cut proximal to the spinal ganglions, all the motor fibers degenerate but the sensory fibers remain intact.

The hypogastric plexus produces vasoconstriction of the blood vessels of the internal genital organs and it inhibits the secretion of the genital glands, whereas the parasympathetic nerves produce the opposite effect. Section of the superior hypogastric plexus does not alter the normal menstrual cycle nor does it interfere with uterine contractions during labor. Likewise, section does not

produce glandular atrophy or any disturbances in the motor function of the bladder or rectum. Therefore the nerve fibers of the superior hypogastric plexus are sensory and not motor. They transmit the sensations from the internal genital organs to the medullary centers. Hence resection of the portion of the superior hypogastric plexus above the hypogastric ganglion is a simple way of relieving a patient of severe pain of pelvic origin.

The second question that may be raised concerns the possible harm incident to removal of a portion of the sympathetic nervous system. Ranson (7) states that Cannon and his students completely removed "the sympathetic chain on both sides, from the highest cervical to the lowest sacral ganglion. Such completely sympathectomized cats have lived under laboratory conditions for many months. . . . Everything indicates that almost any part of the sympathetic system can be removed without seriously endangering life."

#### TECHNIC OF OPERATION

The operation described is the one recommended by Cotte (8). Since many of the patients for whom this type of operation is indicated are poor surgical risks, it is best to open the abdomen under direct infiltration anesthesia. The rest of the operation may be performed readily under ethylene or ether anesthesia or even under infiltration anesthesia. The patient should be placed in the Trendelenburg position after a midline incision of 10 to 12 cm. has been made from the umbilicus down toward the pubis. After the peritoneal cavity is opened, the small intestine is packed off and the sigmoid and rectum are pushed to the left side and held there with a wide retractor. The uterus, adnexa and bladder then may readily be inspected and palpated to determine the extent of the malignant infiltration. One may also detect a complication, such as suppurating tubes, that can be remedied by a surgical procedure. The area of the lower two vertebrae and the upper part of the sacrum is exposed to view. In some thin women it is possible to see the presacral plexus immediately beneath the peritoneum. Whether or not the plexus is seen, the parietal peritoneum above and in the middle of the sacral promontory is elevated and incised with scissors. This incision is extended upward and down along the sacrum for about 4 or 5 cm. When the peritoneal flaps are pulled aside, a layer of fibrocellular connective tissue, covered by adipose tissue, will be exposed. This tissue can be separated easily from the peritoneum and the lower end of the aorta without danger. The presacral plexus lies in this layer. With an aneurysm needle the tissue is elevated at the bifurcation of the aorta and the dissection is carried to a still higher level. As this is done, it will be found that in most instances the tissue spreads out triangularly. The middle sacral artery should be pushed away from the plexus, but if it is injured it can be ligated readily.

After the dissection is carried as high as desired, the layer of nerve tissue is separated from the underlying tissue down past the sacral promontory into the pelvic cavity. In this area the plexus is divided into two hypogastric nerves and therefore they must be dissected individually. At least 2 or 3 cm. of each hypogastric nerve should be resected in addition to 4 or more cm. of the superior



hypogastric and the intermesenteric plexuses. The fibrous tissue layer, which contains the hypogastric nerves, is much more resistant than that which contains the presacral plexus. As the dissection is carried out, nerve filaments projecting outward will be encountered. These should be followed as far laterally as possible before they are cut. In most instances ganglions will be included in the resection. It is preferable to remove the dissected tissue in one piece. It is not necessary or advisable to ligate the presacral plexus or the hypogastric nerves before they are cut, because the only blood vessels in intimate contact with them are insignificant vasa nervorum. Very rarely does one encounter bleeding that requires more than simple temporary pressure to check it. Care must be exercised to avoid injury to the inferior mesenteric vessels when the mesosigmoid is extremely short. After the plexus is resected, the posterior parietal peritoneum is sutured with plain surgical gut and the abdominal wall is closed in the customary way. Since women with inoperable carcinomas are usually cachectic and their wound healing is poor, silk worm gut or some other permanent suture material should be used to aid in the closure of the abdominal wall.

#### SUMMARY

A recommendation is made that pelvic sympathectomy be used for the relief of severe pelvic pain in women. There are four definite indications for this operation: (1) severe dysmenorrhea not relieved by medicinal, hormonal and mechanical measures, (2) endometriosis in young women in whom castration is not desirable, (3) operable and inoperable carcinoma of the uterus, tubes and ovaries and (4) severe persistent pelvic pain of unknown origin not relieved by previous laparotomies. The anatomy, physiology and technic of pelvic sympathectomy are discussed.

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# RADIATION THERAPY FOR CANCER OF THE CERVIX WITH AN ANALYSIS OF THE FUNDAMENTAL DOSIMETRY

WILLIAM HARRIS, M. D. AND SIDNEY M. SILVERSTONE, M. D.

(New York, N. Y.)

*From the Department of Radiotherapy and the Tumor Clinic,  
Mount Sinai Hospital, New York.*

During the last fifteen years there has been a steady significant improvement in the five year cure rates of radiologically treated cancer of the cervix uteri. This has been due to a better understanding of radium technic and to the addition of adequate x-ray therapy to points in the pelvis beyond effective range of radium. The establishment of an international unit of measure, the "r" (roentgen), made for a new era in radiotherapy whereby technics could be duplicated anywhere in the world and treatment applied in a more effective and scientific manner. With the improvement in cure rate, follow-up studies revealed that we were encountering a greater number of early and late complications in radiologically treated cancer of the cervix. This was to be expected because normal pelvic structures were receiving much larger doses and, certainly in our early, enthusiastic days, doses far in excess of normal tissue tolerance.

This clearly indicated the necessity for an analysis of various anatomical and physical data which are involved in the radiological treatment of cancer of the cervix. Methods and systems of treatment employed by us and other clinics were examined and it became quite clear that empirical methods with fixed dosage factors contributed largely to a high incidence of injury, morbidity and mortality, often, ironically enough, in patients whose cancers were cured.

It may be stated at the outset that when two physical agents with similar biophysical properties, namely x-ray and radium, are used to treat a lesion simultaneously or within a given period of time, injuries or complications resulting from such treatment, which are not mechanically produced, must be considered a summation of the biophysical effects of the two agents employed. To blame either the radium or x-ray for an injury to normal structures, when both are used to treat the same lesion, is fallacious reasoning.

To properly evaluate the treatment requires a careful physical analysis of the isodose curves of both the radium and x-ray. The actual dosage values may vary little with different technics, yet, if expressed in milligram hours without further qualification, great differences may exist.

For this reason, expression of dosage in roentgens (x-ray and radium) to various representative points in the pelvis is the only method available today for correct understanding of any given technic and this will make it possible to alter the dose according to anatomical variations and to variously sized and placed tumors.

Tables are now available for the computation of doses of linear sources of

radium in variously sized capsules and for those containing different amounts. Similar tables are available for x-rays of varying voltages. Utilization of the above will allow for variations in technic which are necessary in patients with anatomical and pathological conditions which do not conform with textbook picture representations and should avoid some of the complications which will be enumerated.

Radiation therapy for carcinoma of the cervix can be delivered effectively to the cervix, the lower uterine segment, the vaginal vault, the base of the parametria, and the paracervical triangles. Under favorable circumstances, it is possible to extend the zone of effective radiation laterally to include the lateral parametria and the lateral pelvic walls. Rarely is it possible to deliver an adequate dose to para-aortic nodes or any other involved region beyond those already mentioned.

In the experience of most Radiotherapists, a dose of 5,000 to 7,000 roentgens, whether gamma roentgens or x-ray roentgens, if delivered to the tumor within a few weeks, is usually cancerocidal for squamous cell carcinoma. The major limiting factor in delivering this dose is the effect of the radiation on normal pelvic structures which must, of necessity, be included within the volume of tissue irradiated.

To protect normal pelvic structures from radiation injury, the limit of tolerance for each structure must be considered in the plan of treatment. This limit depends in great measure upon the rate of administration of radiation and the over-all treatment time as well as upon the inherent factors of radiosensitivity and radie-resistance. As a general rule, the slower the rate of administration and the longer the over-all treatment time, the greater is the tolerance. Other factors which influence the tolerance of tissues to irradiation are the size of the volume of tissue irradiated and the state of nutrition as affected particularly by infection, anemia, diabetes mellitus, vascular disease, previous pelvic operation or infection, or previous pelvic irradiation. Anatomical changes, especially adhesions of viscera in the pelvis may also be serious limiting factors.

The following structures and regions require special consideration: a. Skin, b. Bladder, c. Rectum and recto-sigmoid colon, d. Paracervical triangles, e. Intestines, f. Femora.

The skin over the lower abdomen, hips, and buttocks, in an average sized pelvis, may tolerate up to about 3,200 r (with back scatter) in the conventional four or six field pelvic cycle technique in which radiation from 200 to 400 KV is administered fractionally over a period of about four weeks, each field measuring about 10 x 15 cm. This dose does not include the exit dose which amounts to about 500 r in a pelvis measuring 20 cm. in its anterior-posterior diameter. The radium therapy also contributes about 500 r. This additional 1,000 r is, however, administered at an extremely low r rate, about 1 r or less per minute for the x-ray and about 0.1 r per minute for the radium. The minimal effect of this additional radiation on skin tolerance is consistent with the well known observation that tissue tolerance is greatly increased as

the r rate is decreased. However, in a pelvis that measures 14 cm. in the anterior-posterior diameter, not only is this additional radiation doubled, but the corresponding r rates are also doubled. Consequently, it must be taken into consideration and the skin dose and the r rates adjusted accordingly. Previous irradiation in particular greatly diminishes skin tolerance, even though the irradiation may have been relatively small in amount and administered many years previously. Irradiation of the skin beyond its tolerance may result in chronic radio-dermatitis, manifested by atrophy, telangiectasia, mottled pigmentation and de-pigmentation, deep subcutaneous induration, and a tendency to the formation of chronic indolent ulcers, keratoses, and even cancer. While chronic radio-dermatitis is an undesirable complication, it is surgically remediable.

The bladder receives a large amount of radiation both from the radium and the x-ray. The most frequent site of radiation injury in this viscus is the posterior wall, just above the ureteric ridge. This portion is anatomically close to the lower uterine segment and the anterior vaginal fornix where vesicovaginal fistulae occur. Radiation injuries to the bladder must be attributed to the summation of the effects of both the x-ray and the radium. The dose from the x-ray therapy varies from 1,500 r to 5,000 r depending upon the technique of application. The dose from the radium therapy is much more variable. It depends not only upon the total number of milligram-hours of radium used in the cervical system but even more upon the geometrical arrangement of the radium and the relative strengths of the various units employed. Generally it is about 5,000 r. However, it may be much more with those systems of radium therapy in which higher concentrations of radium are employed in the cervix than in the fundus or lateral fornices.

Greater doses in the bladder may also occur from certain accidents or errors in the actual technique of application of the radium. For example, the dose at the surface of the intra-uterine tandem may be as high as 20,000 or 30,000 r. If this tandem should project too far out of the cervical os or slip out of the uterus altogether, it may come close to or in actual contact with the anterior vaginal wall. The tandem may also be brought closer to the bladder if the uterus is anteфлекed. If the anterior lip of the cervix is destroyed by disease, the lower end of the tandem may actually lie against the anterior vaginal mucosa. End-radiation from the tandem must also be considered if the uterus is rotated so that the cervix points anteriorly. Another example of danger is malposition of the vaginal applicator, the surface dose of which may be as high as 20,000 r. The correct position for this applicator is either against the cervix itself or in the lateral fornices where such high doses can be tolerated. If this applicator is not maintained firmly in proper position, it may shift or rotate into the anterior fornix where the bladder would then be subjected to a higher dose of radiation than it could tolerate. Still another example of danger lies in interstitial methods of radiation, not only from accidental displacement of needles or seeds, but also from a direct application in the anterior fornix.

The limit of tolerance for the bladder must be below 10,000 r. In cases in

which bladder injury has occurred, it has been calculated that the posterior bladder wall received more than 10,000 r. There is probably a large individual variation in bladder tolerance. The incidence of bladder injuries is high, the reports varying from 6 to 14 per cent in large series of cases. The condition of the bladder mucosa is probably a major factor and for this reason it is advisable to do a preliminary cystoscopy in all cases, before any form of treatment is instituted.

The rectum also receives a large amount of radiation both from the x-ray and the radium and rectal injuries must therefore be attributed to the summation of the effects of both. Anatomically, the rectum and the recto-sigmoid colon are close to the cervix and lower uterine segment, and the recto-vaginal septum is frequently thin. The most vulnerable region of the rectum appears to be the anterior wall, about 7 to 10 cm. from the anus. This region of the rectum receives about the same dose from the x-ray and the radium as does the posterior wall of the bladder that is 1,500 r to 5,000 r from the x-ray and about 5,000 r from the radium. As with the bladder, the radium doses to the rectum are subject to variation in a similar manner. Higher doses in the rectum may be obtained if radium systems of high concentration in the cervix are employed. The same type of accident or error in the technique of application which produces a high dose in the region of the anterior fornix may produce a high dose in the posterior fornix. A projecting or slipped tandem may lie against the posterior vaginal wall or a vaginal applicator may be displaced into the posterior fornix. Closer approximation of the tandem to the rectum and recto-sigmoid colon may occur if the uterus is retroflexed. End radiation from the lower end of the tandem must be considered if the cervix points posteriorly. Interstitial methods of irradiation are similarly hazardous, especially if the region of the posterior fornix is the site of implantation. According to Paterson and Parker, the limit of tolerance of the rectum is below 10,000 r.

The paracervical triangle was defined by Tod and Meredith as that portion of the parametria included between the vault of the vagina and the lateral wall of the uterus. It consists essentially of loose areolar tissue, fibrous tissue, and blood vessels, and contains the ureter as it courses towards the bladder. Anatomically, the paracervical triangle is continuous in the same fascial plane with the vesico-vaginal and recto-vaginal septa and with the extraperitoneal fascia of the pelvis. Overdosage in the paracervical triangle results in radionecrosis of the connective tissue complicated by an extensive chronic inflammatory process which may spread in this fascial plane, fix the uterus, and encircle and constrict the lumen of the rectum. According to Todd, this injury may appear six months to two years after treatment and simulate a recurrence of neoplasm. Further complications are stenosis of the rectum and recto-vaginal fistula. On the other hand, stenosis of the ureter is rarely the result of treatment, but, more commonly, the result of infiltration by neoplasm. It can, however, be produced experimentally in dogs by radium needle implants. The paracervical triangle receives about 6,000 r to 7,500 r from the radium therapy and 2,000 r to 4,000 r from the x-ray therapy. According to Tod and Mere-



dith, the limit of tolerance is about 9,000 r to 10,000 r, if delivered in about six weeks. It is extremely important to recognize this form of injury when it occurs. A mistaken diagnosis of recurrence of neoplasm may lead to the administration of more radiation, with disastrous results.

The small intestine and the colon are radiosensitive, but intestinal injuries are less common than might be expected, possibly because intestinal movements prevent constant irradiation of the same loop of bowel. When intestinal injury does occur, there is often the history of a previous pelvic operation or inflammatory condition which resulted in adhesions of one or more loops of gut in the pelvis. A cervical stump is a common site for such adhesions. The usual form of radiation injury of the bowel is a localized radiation ulcer which may either perforate and produce a peritonitis or heal and produce a stricture. Sante recommended pneumoperitoneum with Trendelenberg position to displace all movable loops of gut out of the pelvis. This procedure also had the advantage of eliminating roentgen sickness and, with the aid of barium, it could be used to demonstrate adhesions of bowel in the pelvis. It is difficult to estimate the relative role played by x-ray and radium in the production of intestinal injuries. Prolongation of the over-all treatment time appears to be the single major factor in the prevention of these injuries. Corscaden, Kasabach, and Lenz reported that the incidence of intestinal injuries in their cases fell from 8.7 per cent to zero when the only essential change in technique was the prolongation of the over-all treatment time, the total dose remaining approximately the same.

The head and neck of the femora are usually included in the direct x-ray beam and may receive 2,500 r from the anterior and posterior pelvic fields. The radium therapy contributes about 500 to 700 r. Lateral fields may add another 2,000 r, thus bringing the total dose to over 5,000 r. Other supplementary pelvic fields such as the sciatic and the obturator fields contribute large doses to the bones of the pelvis. Strauss and McGoldrick reported a series of cases of fractured neck of femur due to irradiation in which a dose of about 5,000 r was delivered to this region of the femur in almost every case. The limit of tolerance for the neck of the femur must therefore be below 5,000 r. Radiation injuries of the pubis, ischium, and ilium have also been reported but they are much less frequent. The injuries to the bones may be attributed, for the most part, to the x-ray therapy, since the contribution from the radium is relatively small.

In order to analyze the x-ray and radium dose distribution within the pelvis, six representative points have been selected where a calculation of the doses from the x-ray and radium therapy would be significant in determining whether or not the tumor is adequately irradiated or the limits of tolerance of normal structures are exceeded: 1. Point A, in the paracervical triangle, 2 cm. from the axis of the uterus and 2 cm. from the vault of the vagina. 2. Point B, in the lateral parametrium, 5 cm. from the axis of the uterus and in the plane 2 cm. from the vault of the vagina. 3. Point C, in the cervix, 1 cm. from the cervical canal and 1 cm. from the vault of the vagina. 4. Point V, in the posterior wall

of the bladder, 2.5 cm. from the cervical canal. 5. Point R, in the anterior wall of the rectum, 2.5 cm. from the cervical canal. 6. Point F, in the head of the femur, 10 cm. from the axis of the uterus.

Points A and B were originally described by Tod and Meredith. The dose at point A is representative of the doses obtained at other points in the paracervical triangle. Point B corresponds to the region of the obturator lymph node in the lateral parametrium. The positions given for points V and R are average but, in the individual case, they depend upon the anterior-posterior diameter of the vaginal vault. Point F depends upon the width of the bony pelvis.

In the usual form of x-ray therapy of the pelvis the volume of tissue irradiated measures about 20 cm. in the transverse plane, 15 cm. in the vertical plane, and about 14 to 22 cm. in the antero-posterior plane. If lateral fields are used, the volume is correspondingly increased.

Most of this pelvic irradiation is unnecessary and undesirable. There is certainly no need to include the femora in the direct beams of radiation. The transverse diameter of the female pelvic inlet is given, in most textbooks of anatomy and obstetrics, as 13.5 cm. A maximum width of 15 cm. for the anterior and posterior fields should therefore be sufficient for almost any female pelvis and would, at the same time, eliminate most of the direct radiation to the femora.

The problem arises as to how much x-radiation should be directed to the cervix because the bladder and the rectum are unavoidably irradiated at the same time. It is generally recognized that x-radiation directed to the cervix, preliminary to the application of radium, causes marked improvement in the appearance of the cervical neoplasm. This improvement is due mainly to the reduction of the secondary infection so frequently present in these lesions. In our experience, one or two weeks of preliminary x-irradiation of the pelvis with anterior and posterior fields 15 cm. wide effect enough regression of the secondary inflammatory process to make the application of radium a safer and more accurate procedure. The dose to the cervix at this stage of the treatment varies from 500 to 1,000 r. It is possible in some cases for penicillin or sulphathiazole therapy to accomplish the same result. Intravaginal x-radiation may also be applied for the same purpose, but, in our experience, the use of the intravaginal cone is limited to a few unusually favorable cases in which the cervical lesion lies completely within a cone inserted into the vagina.

Since a well planned system of radium therapy can deliver an adequate dose to the cervix and its immediate vicinity, it is for the disease in the lateral parametria that further x-ray therapy is of value and it is in this region that the doses from both the x-ray and the radium supplement each other to produce a cancerocidal effect. In order to diminish the amount of radiation to the midline structures, which include the bladder, the cervix, and the rectum, Arneson and Quimby recommended a four field technique, two anterior and two posterior, with a separation of 2 cm. in the midline between the two anterior fields and a similar separation between the two posterior fields. Cade recommended a 4

cm. separation. Tod and Meredith employed a 5 cm. lead strip in the middle of an oval cone 15 cm. wide, thus producing two narrow slightly divergent beams directed to the parametria. By their method, not only the midline structures but also the femora were spared direct radiation. This method of directing x-radiation only to the parametria was further investigated by Silverstone, Braestrup, and Wolf, who made depth dose studies for a 15 x 15 cm. field divided by a centrally placed lead strip, 4 cm. wide, into two narrow fields, 5.5 x 15 cm. each. A width of 4 cm. was chosen for the central lead strip because the radium therapy can be made adequate for a region 4 to 5 cm. wide at the level of the cervix. Roentgenograms of the pelvis made with the divided beam illustrate the sharp localization of the direct beam to the lateral regions of the pelvis. The midline structures are completely spared direct radiation while only a small portion of the head of each femur is included.

The depth doses obtained at the six representative points with various techniques in a pelvis 20 x 32 cm. in size, irradiated to the limit of skin tolerance, are shown in Table I. The smaller size of the fields in the divided field technique permitted an increase of the skin tolerance dose to 3,000 r, measured in air, compared with 2,400 r for the 10 x 15 cm. fields. The lateral parametrium dose at point B, is approximately the same for all techniques, about 3,000 r. If the beams are angled 10 degrees inwards towards the midline, or directed parallel to each other, without separation, a dose of about 4,500 r is delivered to the bladder, cervix, and rectum. As the beams are separated from each other, the doses to these midline structures are reduced. At 2 cm. separation they average about 2,400 r. At 4 cm. separation, they are reduced to about 2,000 r. The lowest dose, 1,600 r, is obtained with the divided field technique. In all techniques employing 10 x 15 cm. fields, the dose to the femur at point F, is approximately the same, about 2,500 r, except for the angled fields. With the divided field technique, the femur dose is not only reduced to 1,200 r, but it is also limited only to the medial portion of the head (fig. 1).

In Table I, there are also included the depth doses obtained with the addition of lateral pelvic fields irradiated to full skin tolerance. The chief value of the lateral fields is that they increase the dose to the lateral parametria by about 1,600 r. Their disadvantage lies in the large dose delivered to the head, neck and trochanters of the femora. Other supplementary pelvic fields, such as the sciatic and obturator, also include the head and neck of the femur in the direct beam.

Almost all of the well known systems of radium therapy for carcinoma of the cervix utilize intra-uterine and vaginal applicators. The intra-uterine applicator is usually in the form of a tandem containing one or more capsules of radium. There is more variety in the vaginal application which may be in the form of ovoids, corks, boxes, plaques, bomb or colpostat placed against the cervix or in the lateral fornices or both. One system employs only interstitial radiation in the form of needles. Nearly all of these systems provide effective radiation to the cervix and immediately surrounding tissues but differ from one another mainly in the dose delivered to the lateral parametria.

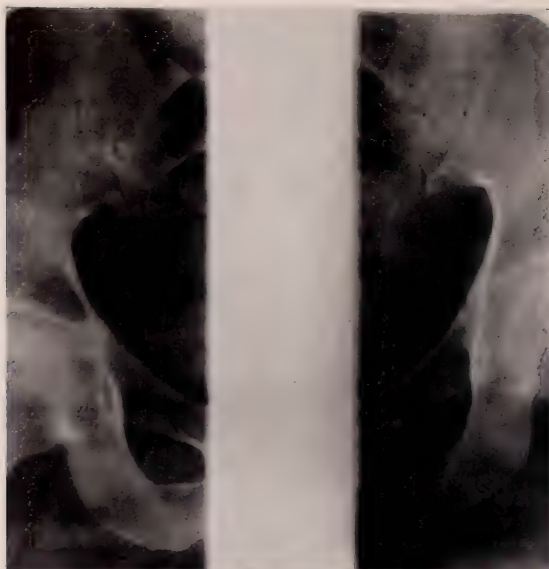


FIG. 1. Roentgenogram of the pelvis made with the x-ray beams employed in the divided field technique.

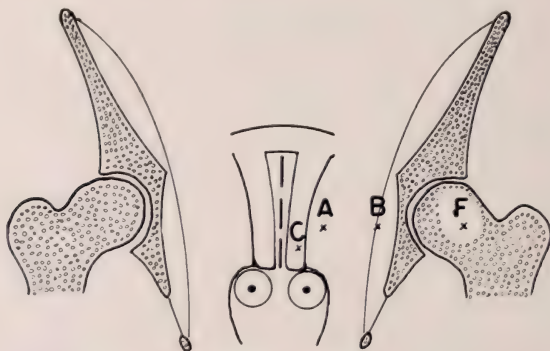


FIG. 2. Diagram of pelvis illustrating location of points A, B, C, and F

The volume of tissue which must be effectively irradiated in order to eradicate a carcinoma of the cervix should include the lower uterine segment and the parametria. Geometrically, this corresponds to a cone with a wide elliptical base. The height of the cone corresponds to the length of the uterine cavity, usually about 7 cm. The elliptical base has a long diameter corresponding to the transverse diameter of the parametria, at least 10 cm., and a short diameter, corresponding to the anterior-posterior measurement of the vaginal vault, about 5 cm. An effective system of radium therapy should have isodose contours approximating this geometrical figure.

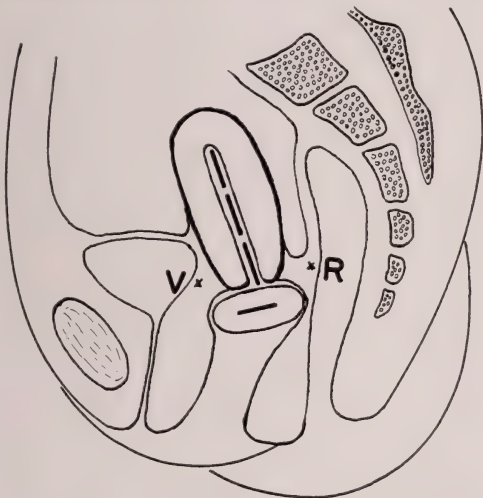


FIG. 3. Diagram of pelvis illustrating location of points V and R

Unfortunately there are many systems of radium therapy employed today in which the isodose contours approximate a sphere rather than the elliptical cone. These are the systems which employ a high concentration of radium at the cervix. In one system, for example, the intra-uterine tandem is composed of two radium capsules, the one in the cervical canal having twice the strength of the one nearer the fundus. The vaginal application is made with an applicator against the cervix and its relation to the vaginal vault is therefore central. The uterine cavity is often not irradiated for its entire length and the lateral fornices may be either neglected or irradiated relatively weakly. The chief criticism of this system of radium therapy is that the dose in the lateral parametria (point B) is relatively small compared with the dose in the paracervical triangles (point A) and that any attempt to increase the dose in the lateral parametria by increasing the total number of milligram-hours in the cervix systems would at the same time increase the dose to the bladder, rectum, and paracervical triangles to a dangerously high level.



In recent years, notably due to the influence of the British school of radiologists, there has been an attempt to develop a system of radium therapy which has isodose contours more nearly approximating the usual local distribution of the disease, that is, the contour which we have described as an elliptical cone. In order to obtain such an isodose contour, an intra-uterine tandem and two vaginal ovoids are employed with radium capsules which bear a definite strength ratio to each other. The tandem occupies the full length of the uterine cavity. The strength of the radium capsule at the cervical end of the tandem is less than that of the capsules in the body of the uterus. If, for example, the

TABLE I

*X-ray dosage at representative points in pelvis calculated from various techniques described in literature*

	TWO ANTERIOR AND TWO POSTERIOR FIELDS 2400 r (in air) per field. Size of field: 10 x 15 cm.				TWO ANTERIOR AND TWO POSTERIOR FIELDS 3000 r (in air) per field 5.5 x 15 cm. each. (15 x 15 cm. field with 4 cm. central lead strip.)	TWO LATERAL FIELDS 2400 r (in air) per field. Size of field: 10 x 15 cm.
	Fields angled 10 degrees in- wards. No separation	Separation of fields at surface (no angulation)				
		0 cm.	2 cm.	4 cm.		
Point V (Base of Bladder).....	4900 r	4700 r	2400 r	2000 r	1600 r	1400 r
Point C (Cervix).....	4800 r	4400 r	2500 r	2000 r	1600 r	1400 r
Point R (Anterior Rectal Wall).....	4900 r	4700 r	2400 r	2000 r	1600 r	1400 r
Point A (Paracervical Triangle).....	3900 r	3600 r	3200 r	3000 r	2300 r	1500 r
Point B (Lateral Para- metrium).....	3400 r	2700 r	2700 r	2600 r	3000 r	1600 r
Point F (Head of Femur)	1200 r	2200 r	2500 r	2600 r	1200 r	2100 r

Calculations were made for a pelvis measuring 20 x 32 cm. and with the following technical factors: 200 KV, 80 cm. target skin distance, filtration of 0.75 mm. Cu and 3 mm. Al, H.V.L. 1.15 mm. Cu.

tandem be composed of three capsules, the relative strengths recommended by Tod and Meredith are 2-2-1, counting from fundal to cervical ends. In the vagina, an ovoid is placed in each lateral fornix, with as much separation between them as possible. The strength of the radium capsule in each ovoid depends upon its diameter in the plane at right angles to the midpoint of the radium capsule. For the most commonly used ovoid which has a diameter of 2 cm., the relative strength of its capsule, according to Tod and Meredith, should be 3. With this 2-2-1, 3-3 system, an isodose contour is obtained which more nearly approximates the usual local spread of the disease, than with any other system. The dose in the lateral parametrium (point B) is approximately one-third of the dose in the paracervical triangle (point A). The actual dose

obtained depends upon the number of milligram-hours of application. Allowing 10 milligrams of radium per unit of relative strength and irradiating for 96 hours, Tod and Meredith calculated that a dose of 7,200 r is delivered to point A in the paracervical triangle. With this arrangement of radium a much greater number of milligram-hours of radium may be safely employed than with any of the spherical contour systems.

It is obvious from this analysis that a statement of the number of milligram-hours of radium has no meaning as an expression of dosage unless it is accompanied by a description of the geometrical arrangement of the radium and of the relative strengths of the units employed so that a calculation in gamma

TABLE II

*Example of summation of x-ray and radium doses at representative points in a pelvis measuring 20 x 32 centimeters*

	V BASE OF BLADDER	C CERVIX	R ANTERIOR RECTAL WALL	A PARA- CERVICAL TRIANGLE	B LATERAL PARAMETRIUM	F HEAD OF FEMUR
Pre-radium x-ray therapy.....	940 r	900 r	940 r	880 r	820 r	310 r
Radium therapy..	4900 r	13000 r	4900 r	6730 r	2110 r	610 r
Post-radium x-ray therapy.....	1140 r	1140 r	1140 r	1670 r	2200 r	880 r
Total.....	6980 r	15040 r	6980 r	9280 r	5130 r	1800 r

Pre-radium x-ray therapy: Anterior and posterior pelvic fields, each measuring 15 x 15 cm. Dose of 800 r (in air) to each field at rate of 200 r daily to alternate fields. Factors: 200 KV, 20 ma, 80 cm. target skin distance, filtration of 0.75 mm. Cu and 3 mm. Al. H.V.L. 1.15 mm. Cu. Treatment time: 9 days.

Radium therapy: Intrauterine tandem containing 40 milligrams of radium element in three capsules arranged 15-15-10 from fundal to cervical ends with filtration of 1.0 mm. Pt. and overall active length of 6 cm. inserted for 90 hours (3600 mgm. hrs.). Followed by vaginal colpostat containing 50 milligrams of radium element, 25 in each cork which measures 2 cm. in diameter, inserted for 90 hours (4500 mgm. hrs.). Treatment time: 8 days.

Post-radium x-ray therapy: Anterior and posterior divided pelvic fields, each measuring 15 x 15 cm. with centrally placed lead strip 4 cm. wide, so that fields are 5.5 x 15 cm. and are directed towards the parametria. Dose of 2200 r (in air) to each field at rate of 200 r daily to alternate fields. Treatment time: 25 days.

Overall treatment time: 42 days.

roentgens may be made. Methods for this calculation have been published by Sievert, Laurence, Wolf, Quimby, Silverstone, and others.

The final analysis of dose distribution is made by the summation of the x-ray and radium doses at the six representative points in the pelvis. An example of such an analysis is shown in Table II.

In addition to the analysis of dose distribution, the time factors require some study. Opinions are still divided as to whether the x-ray therapy should be administered before or after the radium therapy. It has been our experience that if part of the planned course of x-ray therapy is administered first, the appearance of the cervix is greatly improved. Often sloughs and protuberant

masses of growth disappear and the cervix assumes a relatively clean granular appearance. When this stage is attained, the x-ray therapy is interrupted and the radium therapy is then instituted. After the radium therapy is completed, the remainder of the planned course of x-ray therapy is given.

The over-all treatment time of the entire course of radiation therapy is about six weeks. The preliminary pre-radium x-ray therapy requires from 10 days to two weeks. It is given through single anterior and posterior pelvic fields, each 15 cm. wide without the central lead strip, for at this stage, irradiation of the cervix is desirable. Generally, not more than 1,000 r is required in the cervix to control the secondary infection and to improve the appearance of the cervix sufficiently so that the radium may be applied accurately and without danger of morbidity. The radium therapy should be planned so that the over-all time of application is about 8 days and the radium is distributed according to the principles established by Tod and Meredith. Following the completion of the radium therapy, the x-ray therapy is resumed with the divided field technique and with such supplementary pelvic fields as the individual case may require. The post-radium x-ray therapy is administered to full skin tolerance over a period of about three weeks so that the entire course of radiation therapy, that is, the pre-radium x-ray, the radium, and the post-radium x-ray, may be completed in about six weeks. The analysis of dose distribution shown in Table II was made from a typical case irradiated according to this plan.

#### SUMMARY

1. The various sites of injury and complications which may be encountered in radiologically treated cancer have been enumerated.
2. A careful history, physical examination and an individualized treatment program is suggested as the most effective method for a high cure rate and low incidence of complications.
3. The use of a short course of x-ray around the pelvis at the beginning will eliminate infection, reduce morbidity and initial mortality and will facilitate the use of radium. Sulpha drugs and penicillin will accomplish the same result and may be used advantageously with preliminary x-ray therapy.
4. Radium is used primarily to sterilize the cervix, vault of vagina and contiguous parametria.
5. Additional x-ray with a cut-out in the axis of cervix, neck of bladder and rectum is used to augment the dose in the parametria.
6. An analysis of commonly used technics has been presented.

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## CHARLES JOHN KIPP

ALFRED M. HELLMAN, M.D.

[*New York, N. Y.*]

About two years ago I received from Dr. and Mrs. W. Byard Long an addition to my Lincoln collection—the original document, signed by Lincoln and Stanton, appointing Charles John Kipp as “Surgeon of Volunteers.” My curiosity was aroused, and after an extensive study I realized that his story, like many another, shows what opportunities there were and probably still are in America for those who have ability and work diligently in their particular fields.

I felt that the story of Dr. Kipp would interest students of medical history in general. Up to now it has been buried in books dealing with his specialty, ophthalmology and otology, from which volumes the following short biography has been gleaned.

Charles John Kipp was born in October, 1835 in Hanover, Germany, where he received his early education. He came to America at the age of 19 and seven years later (1861) received his M.D. at the College of Physicians and Surgeons, Columbia University. The Civil War having started, he entered the Northern Army in 1862 as Acting Assistant Surgeon. In 1863 he was made Assistant Surgeon and in 1864 Major Surgeon, and in 1865 he became Lt. Colonel and Surgeon. In November, 1867 he resigned. His military record was excellent, and he seems to have been given a very good all-around training and to have developed his executive ability as well.

In the Army he served as Assistant Surgeon to the Third Battalion, N. Y. Artillery, as of January, 1862; Assistant Surgeon, U. S. Volunteers, 1863; Surgeon, U. S. Volunteers, 1864, and was “brevetted Lt. Colonel for faithful and meritorious services during the war” (March, 1865).

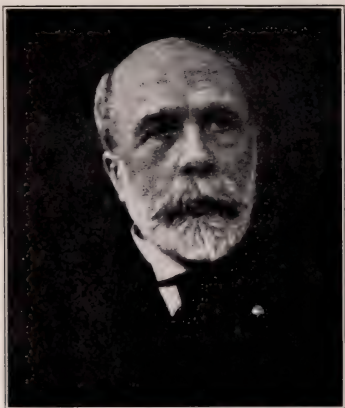
He served in the field until 1863 and after that in hospitals at Nashville, Tenn., and Indianapolis, Ind., and was chief of the U. S. Board of inspectors of recruits at the general rendezvous of the State of Indiana. He also held the position of Medical Director of “Freedmen’s Bureau” of that State from August, 1865, to February, 1868.

In 1869 he settled in Newark, N. J., as an ophthalmologist and otologist. (At that time these specialties were still combined.) It was as an ophthalmologist that he achieved his greatest reputation. In Newark he founded an Eye and Ear Clinic at St. Michael’s Hospital and also founded the Newark Eye and Ear Infirmary. He became Chief Surgeon to the Newark Eye and Ear Infirmary and Consulting Ophthalmological Surgeon to the German, St. Barnabas, Bayonne, Mountainside and Summerset Hospitals.

That he took an active interest in the affairs of organized medicine aside from his interest in routine and hospital practice is evidenced by the fact that he became President of the New Jersey Ophthalmological Society (1865–1866) and from 1901 to 1906 of the New Jersey Tuberculosis Sanitarium. In 1907–1908 he

was President of the American Ophthalmological Society. He also became President of the Otological Society and Vice President of the American Medical Association. He was also a member of the International Congress of Ophthalmologists of Heidelberg in 1894. In 1876 he was elected to membership in the American Ophthalmological Society, the New York Ophthalmological Society and the Essex District Medical Society. In 1875 he became President of the German Hospital Medical Association and one of the Vice Presidents of the New Jersey Academy of Medicine.

Peter Callan of New York wrote of Kipp that "he was the first to recognize the frequent connection between optic neuritis and otitic thrombosis of the lateral



CHARLES JOHN KIPP  
1835-1911

sinus" and "he was the first to report in America a case of *Cysticercus* in the Ocular Conjunctiva."

According to Dr. Harry V. Wurdemann, one of Dr. Kipp's notable achievements in science was his discovery of a form of eye disease caused by malaria, to which he was the first to call attention in the early nineties.

Dr. Kipp was a frequent contributor to medical journals and also to the Medical Encyclopaedias. Perhaps his most important writing was the section on "Diseases of the Ear" in the International Handbook of Surgery.

He died of pneumonia at Newark, New Jersey, on January 13, 1911, at the age of 76. He was active until the last. His photographs showed that he wore a full beard and was bald. It is stated time and again that he was esteemed and loved by all who knew him. He certainly was a keen observer, an honest reporter and an able practitioner.

Listed below are 17 of the articles he contributed to medical literature, and I shall briefly discuss a few of them to give some idea of the variety and calibre of his work.



(To all who shall see these presents greeting.)

**Know Ye** That upon great trust and confidence in the just wisdom, order, policy, and ability of *Charles J. Kipp* I have nominated, and by and with the advice and consent of the Senate do appoint him Surgeon of Volunteers in the service of the United States: to which we wish from the *Twelfth* day of *March* eighteen hundred and *Eighty four*. He is therefore carefully and diligently to discharge the duty of *Surgeon* by doing and performing all manner of things the said duty may require. And he is to diligently and carefully all Officers and Soldiers with whom he may be called out to have done as *Surgeon*. And he is to observe and follow such orders and directions from time to time as he shall receive from me in the future. President of the United States of America, or the General or other superior Officers as we have now doing to the rules and discipline of this. This Commission is continue in force during the pleasure of the President of the United States: the time being

GIVEN under my hand at the City of Washington, *Twelfth* day of *March* in the year of our Lord one thousand eight hundred and *Eighty four* under the *Eighty sixth* year of the Independence of the United States.

(By the President)

*Attest*

*Abraham Lincoln*



Article 1 shows his ability to observe details and marks his thoroughness. At that time Small Pox was, of course, far more common than it is today.

Article 2 is a brief report of an operated case of sarcoma of the eye with mention of two similar cases from the literature.

Article 3 was written, first, to show that recovery from well marked intracranial disease supervening in chronic suppuration of the middle ear is not so rare an event as was commonly believed; second, to advise the use of the ophthalmoscope as an aid in diagnosing intracranial disease.

Article 5 shows fine anatomical knowledge as well as clinical powers of observation.

Article 6. Though he seems to have proved that his cases did not show a marked discrepancy between bone and ear conduction, he admits that his observations may have been faulty, because, as he says, "My patients were not remarkable for their intelligence, and it is not improbable that they mistook vibration for sound."

Article 8. In this article he states, "I find that I have more or less complete notes of seven cases of sparkling synchysis and in all but one of these ear disease was present." His "more or less complete notes" speaks for real honesty.

Article 9 shows that he early noted the close relationship between optic neuritis and cases of purulent inflammation of the middle ear.

Article 10. Here as in No. 9 he shows the close relationship between the eye and the ear, which he stresses further in Articles 11 and 17. Today this close relationship is still worthy of emphasis.

Article 14 might interest neuro-psychiatrists with their new term "psychosomatic medicine." Here he discusses the mental derangement which is sometimes seen in eye hospitals.

Article 16 refers to an article he had written 22 years earlier and describes metastatic panophthalmitis as resulting from infections of other parts of the body, some at a great distance from the eye.

#### CONTRIBUTION BY CHARLES J. KIPP TO MEDICAL LITERATURE

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## THE HUHNER TEST

MAX HUHNER, M.D.

(*New York, N. Y.*)

I was so disappointed with the haphazard method of diagnosis in sterility, not only by the average physician and specialist but by the greatest authorities on the subject thirty years ago that I determined to work out a method wherein fairly exact diagnoses could be made on a purely rational scientific basis.

To illustrate the confusion that existed in the minds of the foremost gynecologists of the time, let me briefly quote as follows. Literally volumes of books and articles were written on the so-called mechanical influences of the various displacements of the uterus and particularly the position of the cervical os as an important factor in sterility in the female. A liberal amount of medical literature was devoted to so-called endometritis and endocervicitis as a cause of sterility. The size and width of the vagina was also assumed to be factors in the prevention of the ascent of the spermatozoa into the uterus. Let us quote Kisch, perhaps the greatest gynecologist of his day, "Sometimes we meet with abnormalities of the vagina—not strictly speaking morbid states which, though they may not at first sight appear to be of much significance, yet suffice to render conception difficult, or even impossible. One of these conditions is extreme shortness of the vagina, in which during coitus the semen is ejaculated at a distance from the os uteri externum; another is excessive length and width of the vagina; another, some displacement of the vagina which diminishes the prospect that the semen will enter the cervical canal." He finally sums up the confused knowledge at the time by saying "How difficult it is, in a particular case, to determine whether the pathological antelexion is the true obstacle to conception, or the antecedent parametritis posterior and the concomitant metritis and endometritis. How can we decide whether a retroflexion is the simple mechanical cause of sterility or whether the later condition does not rather depend upon complicating perimetritis and oophoritis?"

The theory upon which the mechanical etiology of sterility was based is that in certain positions of the uterus, it was supposed that the spermatozoa either could not reach the cervix at all during or shortly after coitus, or, having reached the cervix, they were unable to get into the fundus and parts beyond.

There were some authorities who tried to reason out theoretically the cause of sterility by the relationship of the penis to the cervix during coitus; among these may be mentioned Pajot, Beigel and Fritsch.

If we consider the various postures taken, and the various contortions and muscular movements gone through by both parties during coitus, we must realize that the penis must point at many different angles during the act; we must also recognize how various, probably, are the positions of the cervix during coitus, and after considering all this we can at once appreciate how ridiculous it is thus to reason out theoretically the relationship of the two, and the direction of the

stream of semen at the moment of ejaculation. Clinical experience also shows the folly of such theoretical reasoning, for if we examine women who have given birth to one or more children, we will find among them a considerable number of cases of uterine displacements of every variety; but this will be discussed later on.

In order to develop my method, it was first necessary to determine the normal behavior of spermatozoa ejaculated into the wife's genitals.

When I made the observations which led to the Huhner Test there were no books or pamphlets on the subject and I had to rely on my own investigations as to the behavior of spermatozoa in the female genitals after coitus in normal and pathological cases. These investigations covered a period of about six years and were made by myself in my office in hundreds of cases, carefully examining the females at various periods after coitus and in various normal and pathological conditions. At the end of that time, I had collected a mass of data together with other facts on the subject of sterility, which I finally published in book form under the title of "Sterility in the Male and Female and its Treatment." This was the first series of investigations ever made on a large scale and in systematic manner of the behavior of spermatozoa in the female genitals. It is true that single observations on this subject had been made in previous years by Sims (I believe in four cases) and Hausmann in about twenty cases, but these were simply accidental findings with no attempt to deliberately study the subject on a large scale and make scientific experiments with spermatozoa.

As a result of these studies of the behavior of spermatozoa in the female genitals at various periods after ejaculation in normal and pathological conditions, I brought out a test for sterility, which I called in my book "The Cervix Test," and later elaborated in a special article calling it the "Spermatozoa Test." This test was taken up by other writers, notable by Reynolds, who, in 1915 in an address on sterility read before the Section on Obstetrics, Gynecology and Abdominal Surgery at the 65th Annual Session of the American Medical Association in San Francisco, devoted considerable space to a description of the "Test" and was the first to call it "The Huhner Test" by which name it is now universally known both here and abroad, notably in England.

I will now describe the Huhner Test and show how all the confusing theories on the etiology of sterility vanish quickly with the employment of this Test.

#### THE HUHNER TEST

We order our sterility case to come as soon as possible after coitus. With a glass cannula, to which a bulb or pump is attached, we suck out a small quantity of mucus from the cervix and examine it at once under the microscope. Very often we may see numerous lively spermatozoa after only a few minutes' examination. Yet what a wealth of information is obtained from these few minutes of examination! What do we care whether the cervix is in its normal position or not, or whether we could reason out theoretically that the penis during coitus goes into this cul-de-sac or that, whether the vagina is very short or of excessive width or length—the living spermatozoa on the cervix tell us at once that for that particular penis, the cervix is in the right position to catch the semen. I have

seen very many patients who have been advised by their physicians to assume unusual positions during coitus, with a view of aiding the spermatozoa to reach the cervix. This question is solved at once with the Huhner Test. We need not care if the woman tells us that all her husband's semen runs out of her vagina after coitus, and that that is why she does not become pregnant, for we have positive proof before us that, no matter how much runs out, enough spermatozoa have reached the cervix for purposes of impregnation! What need we care if the woman tells us that she cannot become pregnant because the husband suffers from premature ejaculation, for again we have positive proof before us that he can deposit his semen in the right place.

Now let us suppose, on the other hand, that we find only dead spermatozoa in the cervical mucus, within a few hours after coitus. In that event we order a withdrawal specimen to ascertain whether the spermatozoa came out dead, or whether they were killed later on. If the withdrawal specimen shows nothing but dead spermatozoa, we know at once that the fault is with the husband, and we examine and treat him accordingly.

But if the withdrawal specimen shows lively spermatozoa, we again need not worry about any abnormalities in the position of the cervix or lack of orgasm on the part of the female, or epispadias, hypospadias, stricture or premature ejaculation on the part of the male, or effluvium seminis, or any other condition that is supposed to interfere with the deposit of semen on the cervix, for we know that the semen got there. In such cases we at once make our diagnosis that in this case the sterility is due to vaginal or cervical secretions which are inimical to the vitality of the spermatozoa and we need not subject these secretions to microscopical or chemical examinations for this diagnosis, for we have the physiological proof of the fact right before us.

If no spermatozoa at all are found in the cervical mucus, we know at once, no matter what the condition of the female genitalia is, that the fault lies with the husband even though his withdrawal specimen may be absolutely normal. There are very many conditions in the male in which a withdrawal specimen would be found normal but in which he is nevertheless responsible for the sterility. I need only mention hypospadias and epispadias, where, on account of the abnormal position of the urethral opening, the stream of semen is directed entirely away from the cervix, and, in bad cases, may even be ejaculated entirely outside of the vagina. If the husband suffers from premature ejaculation, his semen will be ejaculated at the commencement of coitus even before the penis has entered the vagina.

But if we do find live spermatozoa in the fundus, we again note the value of the Huhner Test. We can at once exclude any flexion, no matter how acute, as the cause of the sterility, because we know that the spermatozoa have successfully passed the angle of flexion. We must, however, consider the possibility that the flexion, though not mechanically interfering with the progress of the spermatozoa, may still act deleteriously by altering the genital secretions through insufficient drainage.

A few words may not be amiss as to certain points in the technic of the Test.

Of course, the microscope, slides and coverglasses should be in readiness. The instruments should have been sterilized by boiling, but must not be placed in any antiseptic solution, as this might be inimical to the vitality of the spermatozoa. They may, however, be placed on a sterile towel. No lubrication is to be used in inserting the speculum. In case a gynecological examination is to be made at the time, it should be carried out after the Huhner Test is completed.

It is advisable to examine each specimen as soon as procured, and not to take all the specimens at one time and examine them. In many cases the material obtained is quite sticky and dries up rapidly unless examined at once.

It must be noted that the Huhner Test does not interfere with any other investigations. We might in addition investigate the semen itself as to the number of spermatozoa, their mobility and the presence of abnormal forms according to the methods of Moench and Hotchkiss. Neither does it interfere with other methods such as the Rubin Test or Endometrial Biopsy, neither do any of these tests or investigations supplant or do away with the necessity of performing the Huhner Test in cases of sterility.

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## EXTRAVESICAL URETER OPENING IN THE FEMALE

A. HYMAN, M.D. AND H. E. LEITER, M.D.

(*New York, N. Y.*)

Anomalies of the urinary tract are common. Of particular interest are those cases in which the ureter terminates outside the bladder. Many of these patients present urinary incontinence as the predominant symptom and are frequently labeled as psychoneurotics. Any female who complains of urinary leakage in association with a normal voiding rhythm should be suspected of harboring an extravesimal ureteral orifice. The treatment is surgical and a cure can be affected.

In order to appreciate this anatomical variation, it is best to review some of the embryological features. Kilbane and Campbell's descriptions cover this aspect very well. "Early in the life of the embryo, the cloaca represents both the future rectum and the future bladder. It gradually becomes divided by a vertical fold into two compartments, with the anterior of these the allantois and the primitive excretory ducts are connected, while the posterior develops into the rectum." The primitive ureteral buds arise from the posterior wall of the lower end of the Wolffian duct in this ventral pouch where both the Wolffian and Mullerian ducts also empty. In the normal process of embryonic growth and development the ureteral orifices usually ascend to a more cephalad and lateral position with relation to the openings of the Wolffian and Mullerian ducts. The Wolffian ducts eventually give rise to the posterior urethra, seminal vesicles, ejaculatory ducts and vasa deferentia. The Mullerian ducts develop into the uterine tubes, uterus and upper part of the vagina. Failure of the ureteral orifices to shift upwards with growth of the urogenital sinus or if the ureteral openings become incorporated in the evolution of the Wolffian or Mullerian ducts, then ureteral ectopy will result. In the case of a double ureter, one or both of these orifices on one or both sides may become extravesimal openings.

It is thus evident that an ectopic ureteral orifice may be located in the urethra, vestibule, vagina, vas deferens, seminal vesicle or ejaculatory duct. In the male, urinary incontinence does not occur because the ureter never empties distal to the external urethral sphincter. The abnormality in males is discovered in the course of investigations for pyuria (rare) or at post mortem examination. In the female, urinary incontinence is absent when the ectopic ureter orifice is located proximal to the external urethral sphincter. These cases develop symptoms when the affected ureter and kidney becomes infected (e.g. case #3). These patients in whom the ureter opens distal to the external urethral sphincter will complain of urinary incontinence.

In Kilbane's classification the following types of extravesimal ureteral orifices occur:

1. Single kidney with single ectopic ureter.
2. Unilateral duplication of the kidney and ureter with ectopy of the accessory ureter (upper).
3. Unilateral duplication of kidney and ureter with both ureters emptying extravasically.
4. Bilateral duplication of the renal pelvis and ureter with only one ureter ending ectopically.
5. Bilateral duplication with ectopy of both supernumerary ureters.
6. Bilateral single ureters—both with ectopic orifices.

Apparently no cases have been reported where bilateral duplication resulted in ectopy of all four ureters. Campbell states that ectopic ureteral orifices do not open into the uterine tubes or uterine canal but he reports the case of

a child where a ureter emptied into the rectum. This he explains on the basis of faulty division of the primitive cloaca by the urorectal septum.

All patients with urinary incontinence who have a normal voiding rhythm should be suspected of harboring an extravesical ureteral orifice. Thorough investigation of the genitourinary tract will lead to corroboration of the diagnosis. Careful search should be made for the ectopic opening, and if possible it should be catheterized and injected with an opaque medium for radiography. The use of indigo carmine to locate this orifice is usually valueless because of the poor function of the homologous urinary segment. Intravenous urography may give considerable information. One may note (a) failure of unilateral visualization, (b) duplication of one or both kidneys, (c) visualization of a renal pelvis, calices and ureter on one side but a sizable segment of kidney for which a caliceal system is not evident. Cystoscopic examination may demonstrate an absent ureter orifice on one side or a single orifice where a double ureter is visualized or suspected.

The treatment of this condition is always surgical and depends upon the general evaluation of the urinary tract. Obviously, a solitary kidney with a ureter ending extravasically can only be treated by ureterovesical re-implantation or by some form of permanent drainage. Other procedures which are applicable depend upon the pathology (uretero-vesical re-implantation, nephroureterectomy, heminephrectomy and ureterectomy). Ligation of an ectopic ureter is to be condemned.

#### CASE REPORTS

The following cases are examples of three different types of extravesical ureter orifice in the female:

*Case 1.* Mount Sinai Hospital Adm. #526203. Urinary incontinence due to hypoplastic right kidney with single ureter emptying into the vagina.

*History.* D. M., a 32 year old married woman was first seen at the office of Dr. Hyman complaining of a constant leakage of urine for many years. Although she voided regularly and normally about three or four times daily, it was necessary for her to wear a sanitary pad constantly because of the persistent vulvar moisture. On the average, about two such pads were used every twenty-four hours. Other than this symptom she felt perfectly well.

*Examination.* The patient appeared well developed and nourished. The head, neck, heart, lungs and extremities were all normal. Neither kidney was palpable. Inspection of the vulva showed a normal vestibule and external urethral orifice. However, on the anterior vaginal and approximately one inch from the vaginal introitus, there was a tiny nipple-like protrusion of mucosa. From this point, a few drops of urine would trickle from time to time. Indigo carmine given intravenously failed to appear at this opening. An attempt was made to pass a catheter into this orifice but all efforts were unsuccessful. Pelvic examination disclosed a normal uterus and adnexae. The blood pressure was 124 systolic and 70 diastolic.

*Laboratory data.* Urinalysis revealed a specific gravity of 1018, albumin and sugar were absent, and microscopic examination was normal. Hemoglobin was 78 per cent (Sahli) with a normal blood count. Urea nitrogen was 16 mgm. per cent.

A flat x-ray of the abdomen revealed a normal left kidney outline but no definite right

kidney shadow could be observed. Intravenous urography showed a normal left renal pelvis, calices and ureter, but no dye could be seen on the right side.

Cystoscopic examination disclosed a normal bladder mucosa and bladder neck. The left ureter orifice was readily seen and it appeared normal. The right half of the trigone was absent and careful search failed to identify a ureter orifice on the right side. The left ureter was catheterized without difficulty, and indigo-carminc administered intravenously appeared in strong concentration from the left kidney within four minutes after injection.

In view of the above findings, a diagnosis was made of incontinence due to a single right ureter emptying into the vagina.

*Operation.* (Dr. Hyman, Oct. 18, 1944.) Under general anesthesia, a hypoplastic kidney about the size of an olive was found in the right lumbar area. The ureter divided into three major calices which entered the small kidney. A nephrectomy was done with removal of several centimeters of ureter (fig. 1).



FIG. 1. Case 1. Hypoplastic single kidney and single ureter which opened into vagina

Within twenty-four hours after operation the patient's vaginal drainage ceased and her wounds healed satisfactorily.

*Case 2.* Mount Sinai Hospital Adm. #547002. Urinary incontinence due to double kidney on the right side with ureter from the upper half of the kidney draining into the vestibule.

*History.* M. S., a 23 year old unmarried female was first seen on July 23, 1944 at the office of Dr. Leiter complaining of a slight but constant urinary leakage since birth. Except for very rare occasions she did not recall ever being dry for any length of time. The incontinence of urine was both day and night. She voided about every four hours during the day and never had to empty her bladder during the night. Although there were days when one sanitary pad would be adequate to control the vulval moisture, there were other occasions when she would require three or more pads in a twenty-four hour period. Her general health had always been good. She never complained of backache or dysuria.

She had consulted several physicians for this disability and was told that it was due to nervousness. It is of interest to state that her father is known to have a double kidney and ureter.

*Examination.* The patient was an intelligent, well developed and healthy-appearing young woman. No abnormality was found on examination of her head, neck, heart or lungs. The abdomen was normal except that the lower half of the right kidney was palpable. Inspection of the vulva revealed a virginal introitus. The external urethral orifice was normal. Just beneath the external urethra was a tiny opening from which a drop of clear fluid was seen to emerge. Blood pressure was 120 systolic and 80 diastolic.



FIG. 2. Case 2. Intravenous urogram showing large segment of upper portion of right kidney for which no caliceal system is visible.

*Laboratory data.* Urinalysis of the catheterized bladder specimen failed to show any abnormality. Blood count and blood chemistry were normal.

A flat x-ray of the abdomen failed to evidence any opaque urinary calculi; the left kidney outline was normal; the right kidney shadow was somewhat enlarged. Intravenous urography disclosed a normal renal pelvis and ureter on the left side. On the right side the renal pelvis was slightly dilated but the upper third of the kidney failed to show any evidence of a caliceal system (fig. 2), creating the suspicion of a duplication of the pelvis and ureter on that side.

On cystoscopic examination the bladder was normal and only one ureter orifice could be seen on each angle of the trigone. An attempt was made to catheterize the small opening in the vestibule beneath the external urethral orifice. This was unsuccessful. However, a small Braasch bulb could be used to occlude the opening, and through this catheter 20 c.c. of 40 per cent hippuran solution were injected. The patient did not experience pain, and the resultant radiogram showed a fine tract running upwards on the right side of the pelvic cavity into what appeared to be a dilated and tortuous tubular structure (fig. 3). No dye could be seen in the lumbar region or kidney.

From the above findings it was felt that this patient had a double kidney and ureter on

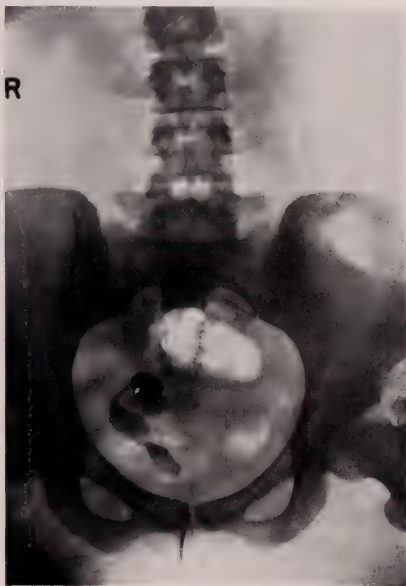


FIG. 3. Case 2. Radiogram obtained after injecting the opening in the vestibule with 40 per cent hippuran solution. Large, tortuous and dilated tubular structure.

the right side with the ureter from the upper part of the kidney emptying into the vestibule. Operation was advised but the patient did not return until March 28, 1946 when she was admitted to the hospital for operation.

*Operation.* (Dr. Leiter, March 30, 1946.) Under general anaesthesia a large right kidney was exposed. The upper fourth of the kidney was a tense, cystic sac with a separate blood supply, and emptied into a markedly dilated and tortuous ureter. The rest of the kidney was normal with a separate blood supply and a normal sized ureter. A resection of the diseased upper part of the kidney with about 20 cm. of homologous ureter was carried out.



The postoperative course was uneventful. The wound healed by primary union. There was no further vulvar moisture. She was discharged from the hospital eleven days after operation.

*Case 3.* Consultation service of the Mount Sinai Hospital. Case #34812. Persistent left sided abdominal pain and pyuria due to an infected left hydroureteronephrosis emptying into the urethra proximal to the external sphincter.

*History.* H. D., a 42 year old married woman was seen at the Consultation Service by Dr. Leiter on May 1, 1946 complaining of frequent attacks of dull pain in the left flank for the past nine years. This pain would persist for several weeks and at times disappear for



FIG. 4. Case 3. Ureteropyelogram resulting from the injection of 40 per cent hippuran solution into the opening within the mid-urethra.

several months. Soon after the onset, she was seen by a physician who advised a urinalysis and reported the presence of pus. Subsequent examinations of the urine always showed pus in varying amounts. At no time did she have chills, fever, dysuria, frequency, polyuria or hematuria. On several occasions the pyuria seemed to disappear with the use of sulfa drugs or mandelic acid. About eight months ago investigation of the urinary tract was carried out and she was informed that the left kidney was absent on the radiograms and that cystoscopic examination showed an absence of the left ureter orifice. Four months ago she saw another urologist who corroborated the above findings but felt that left lumbar exploration should be performed. This was done and it was reported that there was no

evidence of any kidney on the left side. Two months after the operation she had another attack of pain in the lower left abdomen. For some time she complained of a tired feeling and within the past year she lost ten pounds in weight.

*Examination.* The patient was a well developed and nourished woman. There was a well healed scar in the left flank. The vulva, vagina and pelvic organs were normal. Her blood pressure was 120 systolic and 80 diastolic.

*Laboratory data.* Urinalysis revealed a specific gravity of 1010, a trace of albumin, no sugar, and on microscopy a moderate number of pus cells with clumping. The urea nitrogen of the blood was 15.9 mgm. per cent. The electrocardiogram was normal. Fluoroscopy of the chest failed to reveal any abnormality in the heart or lung. The hemoglobin and white blood count were normal. The Kahn test for syphilis was negative.

A plain roentgenogram of the abdomen showed a normal right kidney outline with nothing definite on the left. Excretory urography disclosed a normal right kidney but no evidence of excretion of the dye on the left side.

Cystoscopic examination: The bladder urine was grossly clear. The bladder mucosa was normal. A few small inflammatory type polypi were seen around the sphincter margin. The right side of the trigone and the right ureter orifice were normal. The left half of the trigone was absent and there was no evidence of a left ureter orifice within the bladder. The right ureter was catheterized for 30 cm. without obstruction and indigo-carmin administered intravenously appeared in fairly good concentration through the catheter within a few minutes after injection. The urine collected from the right kidney was clear, failed to show pus, and the right retrograde ureteropyelogram was essentially normal except for a slight dilatation.

In order to explain the source of the pyuria, urethroscopy was then done with the idea of searching for a urethral diverticulum or an ectopic ureteral orifice. A small opening was found in the midline of the urethra and about  $1\frac{1}{4}$  cm. distal to the bladder neck. A #5 fr. ureter catheter could be passed into this aperture for a distance of 30 cm. Aspiration of this catheter yielded 6 cu. cm. of cloudy, purulent fluid. Radiography showed the ureteral catheter to be coiled up in the left side of the bony pelvis. Injection through the catheter of 50 cu. cm. of 40 per cent hippuran solution yielded a radiogram which showed a uretero-hydronephrosis which extended to the lumbar region (fig. 4). Another x-ray picture taken 10 minutes after withdrawal of the cystoscope and catheter with the patient in the upright position revealed that the fluid within the ureter and kidney was trapped.

Nephroureterectomy was advised for this patient and a curative result may be expected.

#### SUMMARY

Urinary incontinence in women with a normal voiding rhythm should make one suspicious of the presence of an extravesimal ureter orifice.

Careful search for the ectopic opening will frequently locate the site of urinary leakage. Catheterization or the injection of opaque material into this orifice are aids in diagnosis.

Three cases were presented of extravesimal ureter orifices. In one, the opening was located in the vagina; in the second, the ureter emptied into the vestibule; and in the third instance, the ectopic orifice was located in the urethra.

The treatment is surgical and the prognosis of cure is excellent.

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## CARCINOMA OF UTERINE FUNDUS

TREATMENT BY HYSTERECTOMY WITH PREOPERATIVE RADIATION WITH RADIUM  
AND SUPERVOLTAGE ROENTGEN THERAPY, AND POSTOPERATIVE RADIATION  
WITH SUPERVOLTAGE ROENTGEN THERAPY

GEORGE KAMPERMAN, M.D.

(Detroit, Michigan)

*From the Department of Obstetrics and Gynecology, Harper Hospital*

It is not the aim of this presentation to discuss all phases of carcinoma of the uterine fundus, nor to make a detailed statistical study of the cases presented. We would rather discuss a few problems presented in the management of the cases reported. Also we wish to record the results of treatment obtained by the use of intracavitary radium and supervoltage roentgen therapy preoperatively, and also supervoltage roentgen therapy postoperatively. The list of cases presented is not large, but all cases represent those treated and supervised personally by one method of treatment. Cases of carcinoma treated personally by other methods will be presented simply as a basis of comparison of results.

The literature on carcinoma of the uterine fundus has become quite voluminous of recent years. Many observers have recorded their experience and results, and a great deal of statistical information has been compiled. Healy (3), Norris (1), Miller (7), Scheffey (2), Masson (4), and many others have given excellent analyses of their work and results. As a result of these and other studies certain fundamental facts have been recorded and are generally agreed to by all.

It is now pretty well established that carcinoma of the uterine fundus is for the most part a postmenopausal occurrence. While a few cases occur during the menopausal change and still a smaller number during active menstrual life, the fact remains that in most cases of this disease the symptoms begin after a period of menopausal amenorrhea has existed.

It is also well established that staining or spotting of blood is usually the earliest of symptoms, rather than an excessive flow. Postmenopausal staining of blood is so often the first symptom of this disease that it is now recognized as imperative that a biopsy (curettage) should be performed in every case of postmenopausal bleeding, either to rule out or confirm the diagnosis of carcinoma of the uterine fundus. This is especially true where the findings on pelvic palpation are negative. Early carcinoma of the uterine fundus presents no findings on palpation. It should be emphasized that the very negativeness of the palpation findings constitute an added reason for suspecting a carcinoma of the uterine fundus. The finding of a fibroid nodule or similar benign pathology should not give one a false sense of security in thinking that the symptoms may all be caused by such a benign lesion. All observers have found the incidental association of fibroids with carcinoma of the uterine fundus so often, that we

dare not assume a diagnosis of benign disease only, because of this presence of a fibroid nodule. The fundamental fact remains that postmenopausal bleeding, regardless of palpation findings, makes biopsy imperative. And no treatment, either by drugs or hormones should delay the obtaining of a biopsy.

Most writers on the subject have pointed out that the earlier the treatment, the more favorable are the results obtained. Healy (3) has shown that with little enlargement of the uterus the results are more favorable than when the uterus is much enlarged. Likewise Miller (7) has pointed to the misfortune of "wasted time" by symptoms being allowed to continue before treatment is begun. The microscopic grading of tumors is also quite generally accepted as being of value in prognosis, although there is some difference of opinion as to its importance, and some pathologists confess difficulty in making satisfactory grad-



FIG. 1. Harper Hospital Case #185322. Gross specimen. Adenocarcinoma of uterine fundus. Clinical grade #I. Histological grade #II.

ings. Although pain is not an early symptom as a rule, Healy (3) has shown that it has a prognostic value.

In studying the cases to be presented we have chosen only those that have been under our personal supervision. That itself limits the number of cases. We find in all a record of 54 cases. These we will place in three groups.

#### GROUP I

This is a group of 16 cases treated by radiation only. The decision to treat by radiation only was chiefly because of inoperability of the disease due to extensive involvement. Here the treatment was merely palliative. Also included in this group are three patients of respectively 73, 77, and 81 years of age. The life expectancy of these patients was not considered great enough to warrant major treatment. In the oldest of these three patients symptoms had been present for only two weeks, but the advancement of the disease was already



so great that operation would have been inadvisable at any age. One patient, #18232, had an early carcinoma but because of a serious cardiac lesion was not operated. She lived seven years after the first radiation. In all she had four series of radiation. During this time interval a series of three endometrial biopsies were obtained. The findings revealed a constant histological grade, there being no evidence of change during the four year period between the first and final curettage (figs. 4b, c, d).<sup>1</sup>

Another patient, #115040, consulted us at the age of 57, having spotted blood for six months. Our advice to perform a diagnostic curettage was disregarded because another physician found no physical evidence of disease. This of course ignored the idea stated previously in this discussion that the very negativeness of findings with postmenopausal bleeding should demand a biopsy. This patient returned to us 12 years later, at the age of 69, challenging our previous suspicions because she had survived so long. However she had been bleeding continuously all this time and examination now showed a frozen pelvis and she died the following year after developing urinary and fecal fistula via the vagina. These two cases illustrate the possible slow growth of adenocarcinoma of the uterine fundus.

Of these 16 cases only two are alive to our knowledge. Several women, untraced, are presumably not alive. One patient, alive ( $3\frac{1}{2}$  years after radiation), is a patient who was curetted in another hospital. Due to hospital crowding the patient was discharged from the hospital before the biopsy report was received and the gynecologist in charge was not aware of the diagnosis recorded on the chart. When later the facts were discovered the patient consulted several physicians, and she was rather averse to treatment because she had no further bleeding. Re-examination of the biopsy slide by other pathologists confirmed the diagnosis of adenoma malignum. She was finally treated by radium and supervoltage roentgen therapy. A 50 mg. tube of radium was allowed to remain for 96 hours. This large dosage was administered because it was thought that the patient's obesity would make roentgen therapy ineffectual. She weighed 275 lbs. For this reason operation was not considered advisable. When the radium was inserted a curettage was again performed and the curettings showed no evidence of carcinoma. There are doubtful cases reported where a curettage has resulted in apparent cure. This patient is alive and free from symptoms  $3\frac{1}{2}$  years after the radiation treatment.

Another patient, #229939, whose age was 77 years when first seen, was given two series of treatment with radium and supervoltage roentgen ray. She is alive and well now at the age of 83, without signs or evidence of recurrence.

In general we would say that radiation alone is proper treatment only for an occasional patient when surgical operation presents too great a hazard.

<sup>1</sup> Since the preparation of this manuscript almost a year has elapsed. All patients have had an additional year of survival. All have been rechecked and none have any symptoms or evidence of recurrence.

## GROUP II

## HYSTERECTOMY WITH POSTOPERATIVE ROENTGEN RADIATION

This is a group of 14 cases practically all of them treated during the period between 1926-1932 before preoperative radiation became a routine procedure with us. Of this group five are known to have died within a year after operation, and one has been untraced since the operation. These six cases constitute 42.7 per cent of this group.

Seven cases are known to be alive and well today and free from evidence of recurrence. One patient died suddenly twelve years after operation from a coronary sclerosis. At the time of her death there was no evidence of recurrence of carcinoma. All these cases survived from 12 to 19 years after operation with the exception of one, who is now well 6 years postoperatively. This gives a survival rate of 8 out of 14, a percentage of 57.1. One observation we wish to emphasize is that the patients who did not survive had evidence of recurrence or succumbed within about a year after the operation.

TABLE I

*Carcinoma of uterine fundus*  
*Hysterectomy with postoperative radiation*

NUMBER OF CASES	SIX OR MORE YEARS SURVIVAL	DEATH FROM RECURRENCE	PERCENTAGE SURVIVAL
14	8	6	57.1

## GROUP III

## HYSTERECTOMY WITH PREOPERATIVE AND POSTOPERATIVE RADIATION

This group consists of 24 cases. There was one operative death, so the number for postoperative study is reduced to 23 cases. This operative death was incidentally the only postoperative death in the group of 38 patients on whom hysterectomy was performed. This death occurred as a cardiac death six days after operation in a patient who was a severe diabetic as well as a luetic.

In this group of 24 patients the average age was 55 years. Seventeen of these were postmenopausal, three occurred just at the menopause, and four during active menstrual life. The average period of symptoms had been eight months, the longest 24 months, while in four the symptoms had been present only two months. All cases came under grade I clinical classification, the uterus being normal in size, or only slightly enlarged, and none of them as large as a 2½ months pregnancy. This means that clinically they were all early cases. In only eight cases was carcinoma demonstrated in the uterus after hysterectomy.

In seven cases the carcinoma was associated with fibroids. One occurred apparently with a miscarriage, the diagnosis being obtained after curettage for bleeding that persisted after the miscarriage. Diabetes was present in four cases, one of these being in the patient who suffered a postoperative death.

Two patients had lues. Three patients were extremely obese, and a good number were definitely so overweight as to make the operation difficult. Six of these patients had a severe hypertension while eight others had a moderate hypertension. One patient had a serious heart lesion but survived the operation well. Another patient had a severe endometriosis and the adhesions in this case caused great difficulty during the operation. No other patient had pelvic adhesions and we note this in particular in order to refute the prevalent opinion that preoperative radiation may cause such extensive adhesions as to make operation difficult. In no case did we note any peritoneal reaction to radiation. Four of these patients had mild infections of the abdominal wound. There were no cases of femoral phlebitis. The earlier cases remained in bed ten days postoperatively, but more recently early ambulation has been the rule. As a rule the patients have been unaware of the malignant nature of the disease but this offered no serious obstacle to the management of the radiation therapy. It is our policy to acquaint some responsible member of the family with the diagnosis, but we aim to hide the fact from the patient.

It seems to be an established opinion, and one that is generally accepted that various carcinomas exhibit different degrees of malignancy. In recorded studies thus far it seems possible that the prognosis of any given case can be foretold from the microscopic picture of the biopsy slide, and that the clinical course of such a tumor runs more or less parallel to what the interpretation of the grading type would predict. Some pathologists have certain mental reservations concerning microscopic grading of tumors, and are not too enthusiastic unless certain conditions are scrupulously observed. Our pathologist at Harper Hospital, Dr. Plinn F. Morse, responds to our query with the following statement which we quote verbatim:

"The practice of grading tumors by number is open to criticism on several grounds.

"One important objection is that the use of a number assumes a measuring stick or some sort of graduated standard which can be applied to the specimen and the result read off.

"This measuring stick exists only in the mind of the pathologist who does the grading and can not be reproduced for comparison with that which some other pathologist may have built up in his own mind.

"The diagnosis of the degree of malignancy for the purpose of prognosis is a very complicated question and the opinion which any pathologist expresses relative to a particular case is made up out of a composite of his individual past experience, the microscopical features of the tumor cells, the reaction of the surrounding tissues, such as connective tissue reaction, lymphocytic infiltration, accompanying degenerative changes, the gross appearances presented in the patient, the patient's age, the rapidity of tumor growth and sometimes other factors.

"Beyond this is another unknown factor which can not be evaluated by any methods at present in our possession. That is the constitutional or immunologi-

cal resistance which a particular patient may possess to destroy, slow up, wall off, or prevent the metastasis of a neoplasm. Differences in the patient's reaction and in the clinical course of microscopically similar tumors in different hosts are commonly observed. The constitutional capacity to resist neoplasia varies from host to host.

"If only the degree of anaplasia of the tumor cells themselves, their nuclear peculiarities, the number of mitoses, etc. were considered, some empirical number might be assigned as a grade for each tumor which would be fairly consistent between one pathologist and another; but when we remember that the organ from which the neoplasm arises modifies the prognosis, on these criteria we are still on uncertain ground.

"Moreover departures from normal cell appearance may be due to embryonal lack of differentiation or to anaplastic retrogression of previously normal cells and again we have to shift our co-ordinates depending upon which of the above factors is at work in a particular specimen.

"To come down to a practical application of the method, the impossibility of assigning a number, 1, 2, 3, or 4 to a case, taking into account all the above mentioned clinical, gross, cellular, reactive, degenerative, and tissue—origin factors, it becomes immediately evident that no simple number can be assumed to represent a reliable figure which might be expected to be duplicated by different investigators and a simple number so expressed may be very misleading to the operating surgeon who may assume that the method has more quantitative value than it really possesses."

In general this viewpoint corresponds to that expressed by Ewing (5), although he is somewhat more enthusiastic over the problem than is our pathologist. Ewing expresses the belief that a "parallel exists to a very marked degree between the histological structure and the usual clinical course," but he also emphasized the importance of the clinical information regarding the tumor. He also stressed the personal equation of the pathologist and believes a correct interpretation requires a wide experience in study of cell structures and in the observation of the clinical course of tumors. And while Ewing believes that cell structure will give prognostic information, he also states that grading of carcinomas of the uterus is comparatively a failure as compared with carcinoma in other organs.

With these limitations in mind an attempt has been made to grade the 23 cases of carcinoma that were treated by hysterectomy with both preoperative and postoperative supervoltage roentgen radiation.

In compiling Table III we do not wish to give the impression that we consider two year survivals as evidence that ultimate cure is certain. We compile all cases in this group for the sake of completeness. The facts are that of 23 cases treated by hysterectomy with preoperative and postoperative supervoltage radiation, two have died of recurrent carcinoma. The others are seemingly well and free from evidence of the disease. One of the recurrent fatal cases is among our most recent cases. In all, 38 patients were treated by hysterectomy, and whenever recurrences developed they were always evident within a year after operation.

In all cases classed as grade I there is cell differentiation towards the mature type of glandular cell. All polarity is usually preserved, and there is practically no anaplasia, and no invasive properties are noted. There is no increase in the nuclear chromatin contents and mitotic figures are absent or rarely seen (fig. 2).

Those classed as group II show moderate cell dedifferentiation towards an immature cell type. There is moderate anaplasia, with increased chromatin content of the nucleus. There is a loss of cell polarity, and cells show a moderate growth capacity. There is irregular gland and cell structure, malformation of glands, and usually with desquamation of cancer cells into the lumen of the glands (figs. 3a and b) (see footnote 1).

TABLE II

*Carcinoma of uterine fundus*

*Treatment by hysterectomy with preoperative and postoperative supervoltage roentgen therapy*  
5 year survivals

HISTOLOGIC TYPE	NUMBER OF CASES	5 YR. SURVIVALS	PER CENT
I	7	7	100
II	3	2	66
III	0	0	0
IV	0	0	0
All grades	10	9	90

TABLE III

*Carcinoma of uterine fundus*

*Treatment by hysterectomy with preoperative and postoperative supervoltage roentgen therapy*  
All Cases  
2-13 years

HISTOLOGIC TYPE	NUMBER OF CASES	SURVIVALS	PER CENT
I	8	8	100
II	8	7	87.5
III	7	6	85.7
IV	0	0	0
All grades	23	21	91

Those cases placed in group III show an advanced anaplasia, with marked increase in the nuclear chromatin. The glands usually show an atypical reduplication with loss of stromal elements, generally presenting a picture of compression with some solid sheets of cells, medullary type of appearance. At times metaplasia is seen. The cells and glands show distinct invasive properties, with beginning infiltration of the uterine wall, many of these tumors appearing solid in character. The orderly glandular arrangement becomes indistinct, and is rapidly lost (figs. 3c and d, 4a).

Examination of microscopic sections of the series after irradiation shows an interesting deviation not heretofore noted by us. This consists of an irregular arrangement of the stroma and muscle bundles at the base of the tumor site.



This observation suggests two possible interpretations. First, that papillary carcinoma of the fundus may represent a primary localized malformation of the uterine wall; or second, this irregularity which we have noted may be in the nature of a reactive process which is part of an effort to localize or confine the growth. There is no question that the uterine wall beneath the tumor does

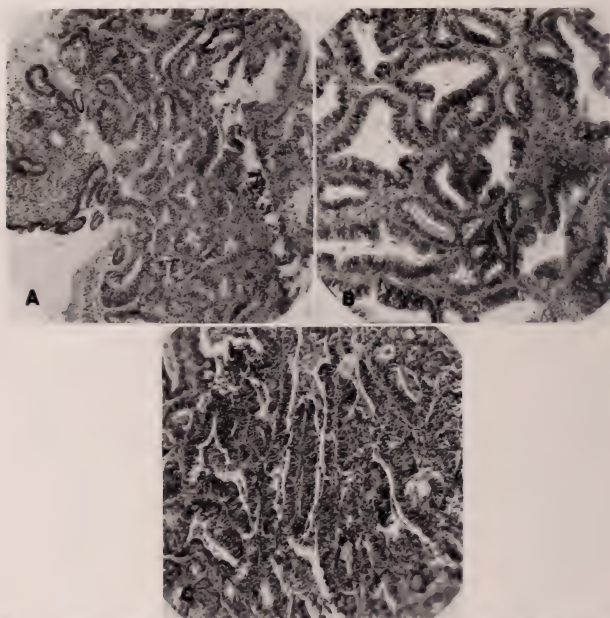


FIG. 2. a. Harper Hospital Case #293323. Photomicrograph  $\times 150$ . Grade #I. Early adenocarcinoma of uterine fundus showing transition from normal endometrium, a portion of which is seen at the left of photographic print.

b. Harper Hospital Case #214134. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Note beginning anaplasia of cells with slight disorientation of endometrial glands.

c. Harper Hospital Case #95496. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Note solid sheets of glands prominently seen in the central areas.

exhibit a definite defensive proliferation of connective tissue comparable to the scirrhous appearance which develops in many epithelial tumors. Accompanying microphotographs show this condition (figs. 5b, c and d) (see footnote 1).

Of the 23 cases surviving the operation two had recurrences and have died. It may be significant that both of these patients had had an artificial menopause established by x-ray for profuse menopausal bleeding, in each case without a

biopsy of the endometrium. However, the bleeding ascribed to carcinoma did not occur until 13 years later in one case, and 20 years later in the other case.

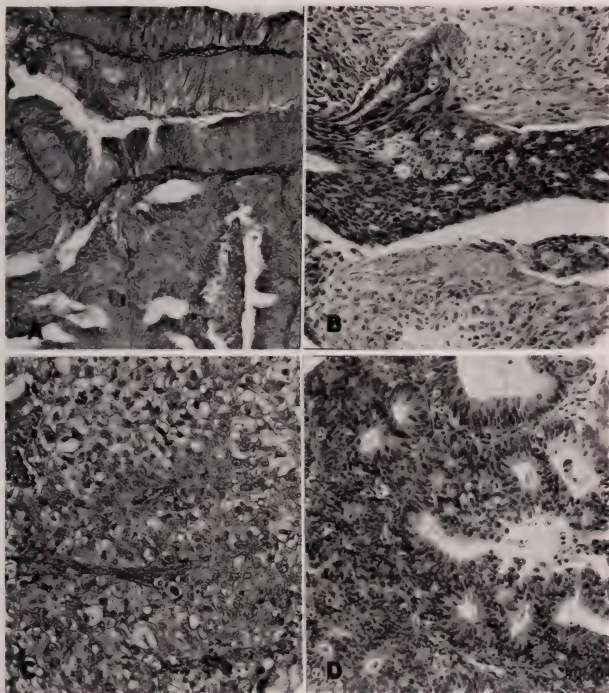


FIG. 3. a. Harper Hospital Case #317870. Photomicrograph  $\times 150$ . Grade #II. Adenocarcinoma of medullary type. Note the tall hypertrophied glandular cells with atypical nuclei especially seen throughout the central fields.

b. Harper Hospital Case #252924. Photomicrograph  $\times 150$ . Grade #II. Squamous type adenocarcinoma of the fundus. The specimen reveals a moderate degree of cellular anaplasia.

c. Harper Hospital Case #308364. Photomicrograph  $\times 150$ . Grade #III: Papillary adenocarcinoma showing an advanced degree of cellular anaplasia with vacuolization of the cytoplasm and a striking increase of nuclear chromatin particles.

d. Harper Hospital Case #259513. Photomicrograph  $\times 150$ . Grade #III. Papillary adenocarcinoma. Note the atypical glandular architecture with cellular anaplasia best seen along the basement membrane.

In both of these patients signs of recurrence were present during the first post-operative year, and both died during the second year after the operation.

If we try to explain the death of these two patients we have difficulty with at

least one of them. Case #164662 was a 57 year old unmarried woman who had an artificial menopause established 20 years before for menorrhagia due to fibroids. After that she had slight bleeding about once every 4 or 5 years.

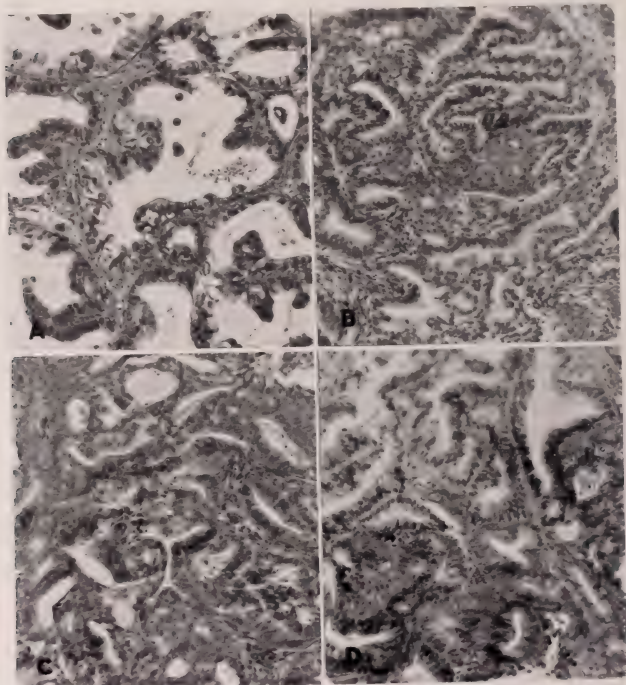


FIG. 4. a. Harper Hospital Case #304477. Photomicrograph  $\times 150$ . Grade #III. Variation in type of papillary adenocarcinoma. Note the striking cellular anaplasia.  
 b. Harper Hospital Case #15231. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Original uterine curettings obtained in 1927.  
 c. Harper Hospital Case #15231. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Curettings obtained in 1929 from same case seen in "b." Note the same histological grade.  
 d. Harper Hospital Case #15231. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Curettings obtained in 1931 from the same case seen in "b" and "c". The tumor remains relatively constant in histological grade.

In May, 1937 she again began spotting, after 20 years of menopause, and continued to do so for nine months when she applied for treatment. A biopsy by curettage showed an advanced grade II carcinoma of the endometrium. The

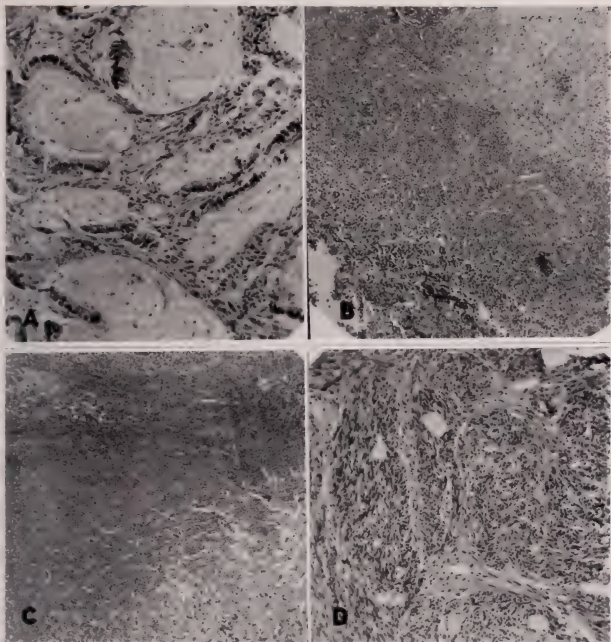


FIG. 5. a. Harper Hospital Case #169778. Photomicrograph  $\times 150$ . Colloid adenocarcinoma of colon. Specimen obtained at autopsy from the intestine of same case noted in Figure 6d eight years after treatment of uterine carcinoma. Note that this lesion is an entirely new pathological experience in this case.

b. Harper Hospital Case #319233. Photomicrograph  $\times 100$ . Section of uterine wall obtained at hysterectomy following curettement, radium, and supervoltage roentgenotherapy. At the lower left is seen a strip of necrotic endometrium. Immediately above, a thick layer of proliferative connective tissue separates the changed endometrium from the deeper myometrium. Myometrial hydropic degeneration is seen in the upper right portion of the section.

c. Harper Hospital Case #319233. Photomicrograph  $\times 150$ . Similar section from the same case noted in "b" under higher magnification. The deeper portions of the fibrotic area show the presence of large inflammatory cells best seen at the top of the photomicrographic print.

d. Harper Hospital Case #319233. Photomicrograph  $\times 150$ . Another field taken from the same section noted in "b" and "c". Note the striking myomatous change in the uterine wall. This field lies in juxtaposition to the area of hydropic degeneration clearly seen in "b".

patient was then given supervoltage roentgen treatments, one daily for five days. After this, radium (3600 mg. hrs.), was used intrauterine. Seven weeks later a total hysterectomy and bilateral salpingo-oophorectomy was performed. Two



weeks after the operation, supervoltage roentgen treatments were again administered daily for five days. This type of treatment is fairly standard at Harper Hospital. In most cases, when we are quite confident of the diagnosis, the radium is inserted at the time of the biopsy. In fact that is our preference, but if this is not done then usually the supervoltage therapy is administered first, followed by the insertion of the radium. The aim is to let a little time elapse before invading the uterus the second time.

At operation in this case the uterus was found to be normal in size, freely movable, with atrophic ovaries and tubes. The uterus after removal showed a small pedunculated sub-mucous fibroid high in the fundus, with an extensive ulcerated area. Microscopic sections showed no residual carcinoma.

The patient seemed well for almost a year when her abdomen began to enlarge and it was evident an ascites had developed. Pelvic examination was negative. A laparoscopy was performed and showed everywhere on the peritoneum millet-seed sized white nodules. A biopsy was not obtained. The ascitic fluid had a specific gravity of 1.015. The Revolta test was positive. The cell content showed many mitotic cells. The patient died during the second year after operation.

This was a grade II carcinoma, clinically early, the uterus after removal showed no residual carcinoma, and her early death from metastasis is rather difficult to explain. Other cases, apparently more advanced, have survived. It is probably a question of individual body resistance to carcinoma. It is also possible that the long period of occasional bleeding indicated the presence of a carcinoma longer than suspected, and that undiscovered microscopic metastases were present even prior to operation.

The other death from recurring carcinoma, case #304477, was that of a 51 year old patient, the mother of four children. An artificial menopause had been produced by roentgen ray 13 years before without biopsy. After two months of vaginal bleeding, following 13 years of menopause, a biopsy by curettage was obtained, giving a diagnosis of grade III carcinoma of the uterine fundus. Daily supervoltage roentgen therapy was given for six days, after which 50 mg. radium was inserted into the uterine cavity for 72 hours. Seven weeks later a total hysterectomy and bilateral salpingo-oophorectomy were performed. The operation was without unusual incident. The uterus was slightly larger than normal but still belonged in group I clinical grade. The fundus contained several small fibroids. The endometrium above the internal os revealed a carcinomatous area extending upward 4 cm., and there was myometrial invasion about  $\frac{1}{2}$  cm. deep. The operative recovery was excellent and supervoltage roentgen therapy was administered daily for six days after the recovery.

The patient was well for six months when vaginal staining recurred. A biopsy in another clinic showed a vaginal recurrence, most likely an implant in the vaginal scar. A radium bomb was inserted over this bleeding area. In a couple of months bleeding recurred again and radium was again applied over the vaginal metastasis. Soon after this x-ray showed metastatic infiltration of the lungs. This progressed rapidly and the patient died about  $1\frac{1}{2}$  years



after the first treatment, with marked pulmonary involvement. In this case the death can doubtless be explained by the highly malignant grade of the

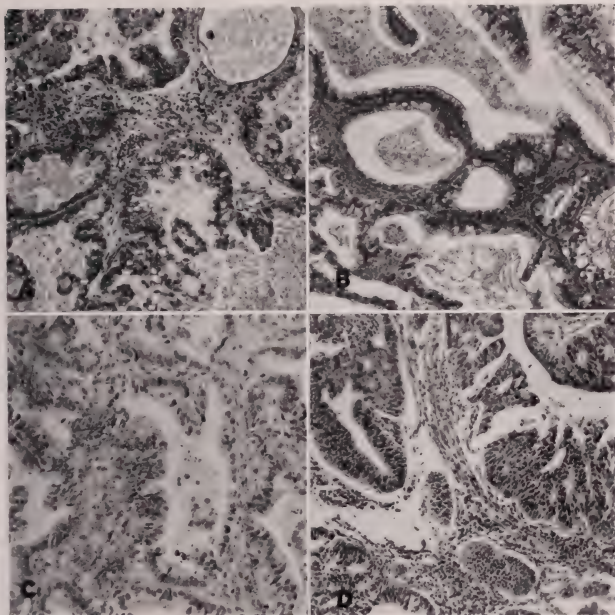


FIG. 6. a. Harper Hospital Case #164662. Photomicrograph  $\times 150$ . Advanced Grade #II. Papillary adenocarcinoma. Original curettings showing a striking degree of cellular de-differentiation and atypical glandular architecture.

b. Harper Hospital Case #304477. Photomicrograph  $\times 150$ . Grade #III. Papillary adenocarcinoma. Original curettings showing numerous mitotic figures along the basement membrane and atypical glandular arrangement.

c. Harper Hospital Case #304477. Photomicrograph  $\times 150$ . Biopsy from a vaginal metastatic lesion of same case noted in "b." A reversion toward quasi-normal endometrial tissue. Note the continued de-differentiation of cellular histology and atypical glandular architecture.

d. Harper Hospital Case #169778. Photomicrograph  $\times 150$ . Grade #I. Papillary adenocarcinoma. Original curettings showing slight anaplastic cellular change with atypical glandular organization.

carcinoma. Accompanying microphotographs show the original tumor and the metastasis (figs. 6b, c and d) (see footnote 1).

In these two fatal cases the clinical course of the recurrence seemed to vary greatly—one metastasizing to the abdomen and causing ascites, while the other resulted in pulmonary metastases.

The general plan of irradiation has been hinted at in these case discussions, and the method of procedure varied according to its combination with surgery and the time of the surgical intervention. The operable cases were operated upon and only the advanced inoperable cases were subjected to radiation therapy alone. In the beginning the procedure was to perform a panhysterectomy first and to administer the radiation therapy postoperatively as soon as the condition of the patient permitted. The disadvantage of this procedure was that since the uterus had already been removed no intracavitary radium could be applied. The insertion of radium in the vagina could accomplish no useful purpose in view of the fact that only a small dose could be given and even so the source of irradiation was too distant from the possible foci of metastasis to have any notable effect. Thus the irradiation had to consist of roentgen therapy alone. An attempt was made to be as efficient as the circumstance would permit in administering the roentgen irradiation and the series was repeated several times. However considering that a large percentage of these cases had a good chance for a permanent cure or a long survival too much damage to the skin and other normal structures from the irradiation had to be obviated. This, then limited greatly the irradiation in its scope.

Later this procedure was changed. A full course of radiation therapy was given first, the operation performed six weeks later and some additional irradiation undertaken postoperatively. By so doing it was possible to increase the dose by applying radium within the uterus in conjunction with the external roentgen therapy. Due to the very rapid falling off of the intensity of the radium irradiation toward the periphery of the pelvis the uterus containing the carcinoma received several times the dose that would reach the bladder, rectum or other vital normal structures. By careful isodose mapping and by changing to some extent the technique of the roentgen cross-firing it was even possible to raise the dose on the parametria to considerably above what could have been given by roentgen therapy alone. Therefore, a combination of intracavitary radium and external roentgen therapy seemed to represent a considerably more efficient method of irradiation than roentgen therapy alone.

In all cases a second series of roentgen therapy, without radium, was given two to three weeks following the operation. Rarely, when there was evidence at the operation that pelvic metastasis had already taken place, a third series of roentgen therapy was added eight or ten weeks after the completion of the second series.

Since 1932 supervoltage roentgen therapy instead of deep roentgen therapy has been used almost exclusively for the irradiation of the carcinoma of the fundus uteri. The relative merits of this procedure in all gynecological cancers were discussed in a former study (6). As it concerns the carcinoma of the fundus uteri it was noted that a slight but definite increase in the final results followed the introduction of the supervoltage roentgen therapy.

Although it is not the purpose of this article to enter into a detailed description of the technique of the irradiation a brief mention of the salient factors may be

made. The radium was applied in form of single or multiple tubes with 0.5 mm. Pt. and 1 mm. hard rubber filter, the total dose usually amounting to about 4,000 or 5,000 mg. hrs. No special effort was made to place the radium in contact with all of the active lesion within the uterine cavity since the aim was mostly to secure an effect on the possible extra uterine extension and since the uterus was removed subsequently. The physical factors of the deep Roentgen therapy were: 200 kv. peak,  $1\frac{1}{2}$  mm. Cu., 1 mm. Al, HVL of 1.9 mm. Cu. and an intensity of 20 r/m at 50 cm. std., and of the supervoltage roentgen therapy: 500 kv. (Const.), 7 mm. Cu., 3 mm. Al, 3 mm. celluloid, HVL of 9 mm. Cu. and an intensity of 20 r/m, at 60 cm. std. The dose was calculated so as to reach the maximum that can be tolerated by the surrounding normal structures.

The question of cure of carcinoma is always uncertain. One can view it from various phases. The actual cure of this disease is so doubtful that medical men speak of survivals rather than cures. Most writers take an arbitrary term of five years. If the patient survives that length of time without evidence of recurrence the next hope is that the patient may survive ten years. These figures are chosen arbitrarily, and it is felt that if a patient survives five years without symptoms or findings of recurrence hopes may run high, even though one occasionally knows of a case where a recurrence seemed to develop after many years of symptomless survival. On the other hand in most series the recurrences if they occur seemingly come early as in our small series. Those that had recurrences usually gave evidence of it during the first year and death occurred before two years had passed.

It has been the custom forced on us by tradition that if patients were lost sight of they should be considered as having died of carcinoma. Furthermore, any death in any series, regardless of the cause, was classed as a death due to carcinoma. This blanket diagnosis of the cause of death seems rather senseless and unintelligent. It of course is intended to make mortality statistics more authentic and above reproach, and insures against undesirable embellishment of statistics. It does seem as if medical writers should be credited with more honesty and intelligence, and when such a patient dies of an intercurrent disease after having survived five years or more without symptoms or signs of recurrent carcinoma the death from the intercurrent disease should not be charged to the carcinoma. If it were insisted that such practice be followed, one can see where it would ultimately lead. These patients even though cured of carcinoma will ultimately all die and we then would have no survivals. Masson (4), in his report on carcinoma of the uterine fundus, takes cognizance of this problem. He quotes from the life tables of the United States Bureau of Census as to what the expected mortality was during the ages under consideration, and deducts this percentage from the percentage that actually died, and thus estimates what percentage could be charged to carcinoma.

In this series there were two deaths definitely due to recurrent carcinoma. Both gave evidence of recurrence and there was no doubt about the diagnosis, and both died during the second year after operation. There is also in this series another case, #169778-38, who remained well for eight years following

operation and treatment. She then became ill and examination revealed a carcinoma of the colon, for which she was operated. She died following the operation. A limited autopsy of the abdomen showed no evidence of metastasis in any retro-peritoneal lymph glands and there was no peritoneal evidence of recurrence. Microscopic sections of all these tissues were negative for carcinoma. She did however have a carcinoma of the mucosa of the colon. This projected into the lumen of the gut and microscopically proved to be a colloid carcinoma of the colon. It bore no resemblance to the carcinoma of the uterine fundus removed eight years before. The pathologist believes this tumor was not a metastasis, but represented a new growth, of an entirely different type. The writer appreciates fully the risk of criticism involved if this case is not listed among the recurrences of uterine carcinoma. But considering the findings we believe it is fair and proper to list this patient among the five year survivals, and not record the death as due to recurrence of the uterine carcinoma. Microphotographs of the uterine carcinoma and the colon carcinoma accompany this text (figs. 5a and 6d) (see footnote 1).

#### CONCLUSIONS

1. We are reporting 23 cases of carcinoma of the uterine fundus treated by hysterectomy, with preoperative and postoperative radiation by supervoltage roentgen therapy.

2. Among these 23 cases, two developed recurrences of carcinoma. Both showed evidence of recurrence within the first year, and died during the second year.

3. Of those cases where treatment was administered five or more years ago, 90 per cent survive and are free from recurrence.

4. Of the entire series of 23 patients, 19 are free from recurrence, although about half of them cannot as yet be placed among the five year survivals. Of the entire series 91 per cent are free from recurrence.

5. All cases belonged to grade I clinically, in that the uterus was about normal in size. Clinically all were early cases.

6. According to microscopic grading the series was about equally distributed among grade I, II, and III. Of grade I, survival rate was 100 per cent. One each of grade II and III developed recurrences and died.

7. Among the five year survivals is one patient who survived eight years, and then died after an operation for carcinoma of the colon. This carcinoma of the colon is considered as a new primary carcinoma because of its histologic and clinical characteristics.

8. Among 38 patients of whom a hysterectomy was performed there was one postoperative death.

9. In these cases there was no evidence that the preoperative radiation caused adhesions.

The cooperation of the departments of pathology and roentgenology is hereby acknowledged. All radiation data and discussion has been contributed by Dr. Trian Leucutia,

Head of Roentgenotherapy. Also all information concerning pathologic problems, with grading of tumors, was supplied by Dr. Plinn F. Morse, Head of Pathology. Mr. Frank Ruslander, Head of Photography cooperated in furnishing the microphotographs; and to Dr. Rudolph Lang, Resident in Obstetrics and Gynecology we are greatly indebted for his painstaking collection of material and study of records.

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# RECURRENT CHRONIC SUBDURAL HEMATOMA IN AN INFANT\*

## CASE REPORT

ABRAHAM KAPLAN, M.D.

Chronic subdural hematoma is fairly common during the first two years of life and will be recognized with increasing frequency when this condition is sought for with greater intensity. Any infant who has been progressing normally up to the age of four or five months and then begins to have convulsions, vomiting, restlessness, periods of lethargy and disproportionate enlargement of the head should be suspected of a chronic subdural hematoma rather than congenital hydrocephalus. This is particularly important because chronic subdural hematoma offers a much more favorable prognosis. In the differential diagnosis of these two conditions it is well to remember that the infant with chronic subdural hematoma appears more cheerful, is more intelligent in behavior and seldom shows downward protrusion of the eyeballs. The simple procedure of bilateral subdural tapping through the lateral portion of the anterior fontanelle is the most important step in establishing the diagnosis. There should be no hesitation in performing this valuable and innocuous diagnostic procedure. Only by early diagnosis and prompt treatment will the cerebral damage of this disease in infancy be reduced to a minimum.

It is not until recent years that chronic subdural hematoma in infancy has received the consideration it deserves. Sherwood (1) in 1930 reported nine cases of chronic subdural hematoma in infancy during a period of four years. Two years later Peet and Kahn (2) recorded in detail nine such cases studied and treated within a three year period. Since then the publications of Naffziger and Brown (3), Ingraham and Heyl (4), Coblentz (5) and Rogatz (6) have stimulated further interest in this subject and have focused our attention on the frequency of chronic subdural hematoma in infancy so that now this condition is less likely to be overlooked. Ingraham and Matson (7) during a period of 7 years observed and treated 98 cases of subdural hematoma in infancy. They stress the following: (1) That this condition is common during the first two years of life, (2) that early diagnosis can readily be established and (3) that with a program of treatment they outlined the results have been steadily improving.

The following case of a recurrent chronic subdural hematoma in an infant is reported because no similar instances has been found in the literature and the unusual and interesting operative findings.

## CASE REPORT

*History.* (Adm. #551054) R. S., aged 10 months was admitted to The Mount Sinai Hospital, on July 2, 1946, with an enormous and fluctuant mass over the right side of the head (fig. 1).

The child was born normally and showed no abnormal signs until the age of 5 months. At this time there was noted a rapid increase in the size of the head, widening of the cranial

\* From the Neurosurgical and Neurological Services of The Mount Sinai Hospital, New York.

sutures with the anterior fontanelle enlarging and tense. A fortnight later the child began to vomit, and this recurred two or three times a week for several weeks. There was no fever, lethargy or convulsions. There was no history of trauma.

The child was taken to a hospital in New Orleans on April 20, 1946 where a bilateral subdural tap was performed through the anterior fontanelle. This yielded an ounce of xanthochromic fluid from each subdural space. Five days later a medium sized osteoplastic craniotomy was performed on the left side. A chronic subdural hematoma measuring 1 mm.



FIG. 1. Fluctuant mass on right side of head which readily transilluminated

in thickness and enclosed in a well formed neo-membrane was found over the greater part of the left hemisphere. Though the outer membrane was difficult to remove, because it was adherent and bled profusely, nevertheless the entire hematoma with the enveloping membrane was completely removed. On May 2, 1946 an osteoplastic craniotomy was performed on the right side and an identical chronic subdural hematoma with its neo-membrane was removed. Both sides of the exposed brain appeared normal. For several weeks after operation bloody fluid was aspirated from underneath the scalp on both sides. The fluid ceased to accumulate on the left, but on the right side the fluid at first bloody, became xanthochromic, and then colorless. About 200 cc. of fluid was aspirated almost daily for over four weeks.

Because the family had to move to New York the infant was brought to The Mount Sinai Hospital.

*Examination* on admission showed an alert, active, playful infant whose responses were fairly normal for his age. He appeared comfortable and made attempts at standing. He was not clumsy or retarded. The head was large. The craniotomy wound on the left was flat and well healed. On the right there was the curved scar of the craniotomy wound and a large fluctuant non-pulsating mass 6 x 6 cm. which could readily be transilluminated (fig. 2). The overlying skin was thin and shiny with very fine dilated capillaries and venules. There were no abnormal neurological signs. X-ray films of the skull showed an unusually



FIG. 2. Showing shiny skin and fine dilated vessels

large head with separation of the sutures. The right temporal bone was lifted slightly at the outer and posterior margin of the operative defect. The operative defect on the left was not remarkable. The cerebro-spinal fluid was clear and colorless and under pressure of 240 mm. of water. Intermittent pressure over the mass on the right side of the head was readily transmitted to the fluid in the manometer. Aspiration of the mass yielded 350 cc. of slightly xanthochromic fluid which had a total protein of 120 mg. per cent. After the removal of fluid the bone flap could readily be palpated through the redundant skin. The bone flap was not displaced. Twenty cc. of air was injected into the mass but was not visualized by x-ray.

*COURSE.* Within 48 hours the fluid re-accumulated. Indigo-carmin 1 cc. was then in-

jected into the lumbar space, the head was kept in a dependant position for half an hour. Aspiration of the cystic mass shortly after yielded 360 cc. of reddish brown fluid without trace of the dye. Two days later the infant fell out of bed but showed no ill effects for 48 hours. Shortly thereafter he had a left sided Jacksonian convulsion, involving the left arm and left leg. There were also transient twitchings of the left side of the face. The right pupil was dilated. The fontanelle and cystic mass was tense. To relieve the pressure the mass was aspirated and only partially emptied by the removal of 250 cc. of uniformly bloody fluid. The convulsive movements abated within ten minutes after the aspiration, but the left arm and left leg were limp. Later that afternoon power began to



FIG. 3. Appearance of infant one month after operation

return in the left arm and leg but was soon followed by a right sided convulsion. This time the left pupil was dilated. During the next 24 hours the child was lethargic and more irritable. Over 360 cc. of pinkish fluid was again aspirated from underneath the right scalp. Further delay seemed unwarranted.

*Operation.* Under ether anesthesia the craniotomy wound on the right was re-explored. The scalp was incised through the old scar and immediately there was an escape of 250 cc. of xanthochromic fluid. Lining the under surface of the scalp was a glistening shiny membrane which extended to the margins and over the outer surface of the bone flap. At the posterior margin of the craniotomy wound there was a defect 2 x 2 cm. and through this a fresh blood clot could be seen over the right parietal region. When the blood clot was

removed with suction two cortical veins could be identified as the source of the recent bleeding. The glistening membrane which lined the outer surface of the bone flap was continuous with the neo-membrane of the underlying chronic subdural hematoma. The defect in the bone and dura at the posterior margin of the craniotomy was the channel through which the subdural fluid escaped to form the cyst underneath the scalp. When the bone flap was reflected a well organized hematoma was found covering almost the entire right hemisphere extending from the frontal to the occipital lobe and from the longitudinal sinus to the lower margin of the Sylvian groove. The hematoma was enclosed in a well formed membrane which was adherent to the under surface of the dura and readily removable from the cerebral surface. When the hematoma and all the visible membrane were removed, the brain though it appeared normal, was sunken about  $2\frac{1}{2}$  inches below the dura. With warm saline irrigations the brain was floated closer to the surface. The dura was closed tightly, the bone flap replaced, and the scalp sutured in a double layer. The patient was given a transfusion of 150 cc. of blood.

The post-operative course was smooth. On several occasions small quantities of blood (20 to 60 cc.) were aspirated from underneath the redundant scalp. The wound healed by primary union. The scalp gradually lost its stretched and shiny appearance. One month after the operation the infant was discharged. There were no abnormal neurological signs. The circumference of the head measured 21 inches (fig. 3). Except for one convulsion three weeks after leaving the hospital the infant has shown no evidence of increasing skull enlargement and has remained well. He is now beginning to walk and speak, is cheerful and shows no mental retardation.

#### COMMENT

For some time after admission this patient presented a puzzling diagnostic problem. It was not clear what was the source and cause of the fluid re-accumulation. At first it was suspected that the rapid formation of such large quantities of fluid must arise from a defect communicating with the right lateral ventricle. But against this suspicion was the difference in character of the aspirated cerebrospinal fluids, the failure to visualize the ventricle when air was injected into the cyst, and the failure to find a trace of the indigo-carmin in the aspirated fluid after the dye was introduced into the lumbar subarachnoid space. That such large amounts of fluid, varying so widely in character can have their origin in a chronic subdural hematoma, and escape through a channel arising from a defect in the dura was an unusual and surprising finding. Similar pathological findings in chronic subdural hematomas have not been previously encountered.

#### SUMMARY

An unusual case of recurrent chronic subdural hematoma in an infant is reported which illustrates the importance of removing as much of the neo-membrane as possible. Of unusual interest is the formation of an exceedingly large cyst between the scalp and calvarium lined with a membrane derived from a defect in the dura.

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## RADIATION THERAPY AS A METHOD OF TREATMENT FOR THE RELIEF OF AMENORRHEA AND STERILITY

IRA I. KAPLAN, M.D., B.Sc.

*Director, Radiation Therapy Department, Bellevue Hospital; Clinical Professor of Surgery, New York University College of Medicine; Attending Radiation Therapist, Beth David Hospital, New York, N. Y.*

It was at Dr. I. C. Rubin's behest that a number of early radiation therapists pioneered in the use of x-ray for the relief of amenorrhea and sterility. Being one of the pioneers, I am pleased and honored to join Dr. Rubin's other colleagues in contributing to this special Journal. May it stand as a well-earned tribute to his lifework in medicine.

Since Biblical times nothing has distressed woman more than the inability to bear children. This is one of the saddest conditions the physician is called upon to treat. The history of such a woman is marked by an unrelenting search for relief from sterility, and so poignant is her demand for such relief that she will stop at nothing from legitimate medical methods to voodooism. The methods tried, like the causes of the tragedy, are without number; none deserves to be considered a universal therapy.

In all instances before a patient reaches the radiation therapist she has already been examined by some gynecologist for the patency of the tubes, and in all instances has had some form of endocrine therapy. Therefore, because these women fail to respond to any of the older methods I feel justified in offering as a possible therapeutic cure, x-ray irradiation. Effective not in all cases but in a substantial number, it is a worthwhile procedure, especially when all other means have failed.

This comparatively new system of therapy has been developed upon the basis of our knowledge of the effect of x-ray on human tissues and organs. Halberstaedter (1) in 1905 established the selectivity of x-rays for the ovary. Originally only the destructive effects of irradiation had been considered of therapeutic value. Nowadays, however, since we have a better understanding of the relationship of body functions to irradiation, x-ray therapy is successfully employed to control various endocrine dyscrasias and functions of vital organs.

Functional disturbances associated with gynecologic conditions were among the first of the abnormal phases effectively treated by irradiation. Because this procedure was found, at first, to be a specific therapy for suppressing menstruation, it was quite logically supposed that if properly employed in smaller dosages it might, instead of suppressing the menses, stimulate these functions which, for one reason or another, were dormant or sluggish. Thus it was that x-ray therapy was suggested for the treatment of amenorrhea and sterility.

In 1926 Rubin (2) reported the use of x-ray therapy as a means of relieving sterility associated with habitual amenorrhea. At his suggestion I applied x ray therapy to a young relative of mine who after five years of married life remained sterile despite treatment by every available therapeutic measure. The x-ray treatment was followed by the birth of a normal boy in 1926. Since then I have consistently applied such therapy to many similarly afflicted women.

In 1924 Rongy (3) reported on the use of x-rays for amenorrhea and sterility, and Hirsch

(4) in 1926 reported favorably on x-ray treatment for ovarian hypofunction. In that year too, Wagner and Schoenhof (5) described experimental research concerning the action of small doses of x-ray on the ovaries. However, up to that time no large, consistent series had been presented; this method of treatment was not yet established as the therapy of choice.

In 1931 (6), and again in 1946 (7 and 8) I reported on a fairly large series of cases so treated, and at the present time I am reporting on 381 cases treated by me in private practice, solely with x-ray therapy. The results clearly confirm my original view that irradiation, properly administered would be effective in a large number of instances of amenorrhea and sterility and would not be harmful to either mother or offspring. Since my original 1931 report many other therapists have reported similar findings.

Drips and Ford (9) found irradiation particularly applicable in cases of menstrual irregularity, whereby, excluding all other etiologic factors, an inherent disturbance of the ovaries may be assumed.

Campbell (10), recently summing up the work in this field of therapeutics, stated, "this form of therapy, can, therefore, play a very helpful role to the gynecologists in the management of endocrine dysfunction causing ovarian and menstrual irregularities."

Although clinical results establish the definite value of x-ray therapy there are still some questions as to its exact mode of action in the female. Do the x-rays work directly through the effect on the pituitary? Do they have a stimulating or a mechanical effect on the corpus luteum? Do they rupture a cystic ovarian condition and thus precipitate menstruation? Do they have a direct stimulation effect on the ovaries? And do they exert a general hormone stimulating effect with resulting normalization of the menstrual function and relief of sterility?

It is generally known that the physiological function associated with menstruation and pregnancy is due to a co-ordinated action of the ovaries, uterus, pituitary and thyroid.

Johnstone (11) states that the cause of amenorrhea is highly complex and involves the whole triangular mechanism of the pituitary, ovary and uterus. This inter-relationship between the pituitary, thyroid and ovary has been recognized for many years. Very recently, however, Hartman and Smith (12) who previously definitely demonstrated indispensability of the pituitary to menstrual bleeding, suggested that for the present the pituitary gland can be disposed of as the cause of menstruation. But Lacassagne (13) holds that a definite minimum of anterior lobe is required to maintain normal physiologic balance of ovarian function, but that one-third of the anterior lobe of the pituitary is alone sufficient to preserve genital activity. Mazer and Andrussier (14) emphasize the definite dependence of ovarian function upon the hormonal stimulation from the pituitary. Finkler and Friedman (15) believe menometrorrhagia and amenorrhea are manifestations of progressive stages of ovarian failure and that ovarian hypo-function may be attended by marked pituitary hyperplasia.

However, the Crossens (16) state that ovarian function is activated by the pituitary, and Aschheim and Zondek (17) prove that the pituitary produces its effect only when the ovary is present. According to Allen (18), the anterior pituitary controls and maintains the action of the ovaries, and Novak (19) ascribes this control to the gonadotropic hormones produced by the basophile cells of the pituitary. (Mazer and Andrussier agree with Frank (20) that the normal menstrual cycle depends upon the balanced activity of the two ovarian hormones.)

Beclere (21) was the first to report the effect of roentgen irradiation on the pituitary. Lacassagne has shown that the anterior lobe of the pituitary is most resistant to destruction by irradiation, and that therapeutic irradiation of the pituitary is therefore not harmful. Werner (22) found that roentgen treatment of the pituitary stimulated menstrual reaction and because of this so-called stimulating action Borak (23) suggested pituitary irradiation for mitigating climacteric symptoms of early menopause.

Whether the pituitary can be affected by irradiation so as to induce hormonal effects and thereby bring about ovulation, is still a moot question. There is evidence that treat-

ment to the pituitary in some cases of amenorrhea may cause resumption of normal menstrual function (Béclère, Mayer, etc.). Schwartz (24) reports a case of acromegaly in which menstruation was restored following x-ray therapy to the pituitary. Hartman and Smith studied the effects of such therapy in monkeys and found that monkeys not ovulating before irradiation remained refractory and failed to ovulate after irradiation of the pituitary. However, no injury resulted from such treatment, for one third of the animals did spontaneously ovulate and conceive in the subsequent normal breeding season.

Notwithstanding these experiments, in some instances in humans, positive results have been noted which seemed definitely associated with pituitary hormone influence. At present we are inclined to attach prime importance to the pituitary as a factor in controlling menstrual function. For example these three cases seem to me to be definitely representative of the pituitary influence. These cases had the usual hypopituitary appearance.

*Case 1.* Mrs. A. G., aged 27, was referred on October 27, 1929 for sterility. Menstruation began at 17 and was always irregular at 3 months intervals. The last period occurred on July 10, 1929. Periods were always accompanied with severe pain. She was short, obese and weighed 167 pounds. She was married at 24 and had not conceived. Other treatments having failed she was referred for x-ray therapy. Treatments were given to the ovaries and pituitary on October 27, November 3 and 10, 1929. She menstruated following treatment and became pregnant and gave birth to a baby girl in July 1930.

*Case 2.* Mrs. L. R., aged 27, was referred on September 28, 1943 for sterility. She was very obese and had been taking thyroid, gr. ii per day for a very long period. Menstruation began at 13 and was always irregular; amenorrhea had been present for about 7 years. She married at 24 but had been unable to conceive. She had had numerous endocrine injections and currettings were reported as showing "an ovulatory mucosa." X-ray therapy was administered on September 28, October 5 and 12, 1943. Following treatment she menstruated regularly for 4 months, became pregnant and on October 11, 1945 gave birth to a normal baby girl.

*Case 3.* Mrs. G. W., aged 21, was referred on September 7, 1944 for sterility. She was short, stout, was covered with hair, and was of the hypopituitary type. Menstruation began at 13 and was always irregular at about 3 month intervals. The last was in June 1944. She married at 19½ but in spite of medical care there was no improvement in her condition. She was very eager to have a child. X-ray treatment was administered on September 7, 14 and 21, 1944, to the pituitary and the ovaries. Two months following treatment she menstruated and became pregnant shortly thereafter. On July 24, 1945, she delivered a normal baby girl.

Another example which suggests x-ray action to relieve what appeared to be a pituitary inhibitory effect.

*Case 4.* Mrs. J. L., age 22, was referred for irregular menstruation and sterility on April 2, 1935. Her menstruation began at 14 and was always irregular at 2-8 months intervals. She married at 20 and the last period occurred in December 1934. She was short, obese, with a marked fuzzy growth of hair on chin and body. The uterus was posterior. X-ray treatment was administered to the ovarian and pituitary areas on April 26, May 3 and May 10, 1935. The dose given (measurements were then recorded in skin erythema dosages) to the anterior ovarian areas was 45 per cent, posterior ovarian areas 25 per cent and the pituitary area 25 per cent SED. Regular menstruation followed and on March 30, 1936 she gave birth to a baby girl. Regular menstruation continued and she gave birth to two more girls in 1938 and 1942.

Another seemingly hypopituitary case is the following.

*Case 5.* Mrs. M. R., age 29, was referred for irregular menstruation and sterility on March 22, 1944. Menstruation began at 14 and was always irregular at 3 to 8 month inter-

vals. She married at 26 and the last period occurred in March 1943, an amenorrhea of 1 year. She was diffusely covered with hair and was obese. X-ray treatment was administered to the ovaries and the pituitary on March 22, 29 and April 5, 1944. She responded well, became pregnant and was delivered of a normal baby boy on March 3, 1945.

Frank states that in the normal, mature, fertile woman the ovary secretes two hormones—the estrogenic factor and the progestational factor—and that normal genital function is dependent on the synchronism of prepituitary, estrogenic and progestational blood cycles. Mazer agrees with Frank that the normal menstrual cycle depends on the balanced activity of the two ovarian hormones. Mazer and Andrusier emphasize the definite dependence of ovarian function on hormonal stimulation from the pituitary. Corner (25) states that progesterin, the hormone of the corpus luteum, will help in cases of sterility and habitual abortion caused by lack of corpus luteum, because it acts as a suppressor of menstruation. Experiments discussed by Allen (26) have shown that surgical removal of the corpus luteum brings on menstruation. Perhaps x-ray acts to destroy a persistent corpus luteum as shown in the following case.

*Case 6.* Mrs. B. E., aged 29, was referred for secondary sterility on April 6, 1927. She already had one child 6 years of age but was unable to conceive again. Menstruation began at 11 and was always irregular. The last period was in March 1927, the previous one in October 1926. She married at 22. She was obese and the uterus was retroverted. X-ray treatment was administered to the anterior and posterior ovarian areas on April 6, 13 and 20, 1927. Normal menstruation followed until July 1927 when she became pregnant and on April 4, 1928 was delivered of a normal baby boy.

This case also suggests the restraining action of a persistent corpus luteum.

*Case 7.* Mrs. H. S., age 30, was referred for amenorrhea and sterility on November 9, 1944. Menstruation began at 15, was always irregular, three times per year. She was married at 24 and 2 years later gave birth to a baby and did not menstruate for the next 4 years. X-ray treatment was administered on November 9, 16 and 23, 1944. Normal menstruation followed, she became pregnant again and on October 4, 1945 gave birth to a normal baby girl.

Frequently following a miscarriage, pregnancy fails to take place in spite of all other remedial measures, as exemplified by the following.

*Case 8.* Mrs. H. B., age 22, was referred for sterility on March 12, 1925. Menstruation began at 13½ and was always irregular. The last regular period was January 24, 1925. She was married in March 1924 and became pregnant in July 1924 but miscarried in August 1924. The only subsequent menstruations were in October 1924 and January 1925. When the usual treatment proved unavailing x-ray therapy was administered in March 1925. She responded well, menstruating in April, then became pregnant and gave birth to a normal baby girl on January 16, 1926.

The following is a case of sterility probably due to a persistent corpus luteum.

*Case 9.* Mrs. T. R., aged 26, was referred on January 13, 1943 for amenorrhea and sterility. Menstruation began at 13, was always irregular. She married at 19½ and continued to have irregular periods. However, after 6 months she became pregnant but miscarried 3 months later. She continued to menstruate irregularly and for 1 year, June 1941–June 1942, was amenorrheic. X-ray therapy was suggested because all other methods including curettage had proved unavailing. Treatment was administered on January 13, 20 and 27, 1943 with good results and she gave birth to a normal baby boy on July 9, 1944. Subsequent menstruation has been regular.



The following case probably represents a pituitary insufficiency with a persistent corpus luteum which possibly accounted for the sterility.

*Case 10.* Mrs. B. B., age 24, was referred for amenorrhea and sterility on May 10, 1927. She menstruated at 12½ and was regular until she married at 21 when menstruation occurred at 2-3 months intervals. After marriage she became pregnant but miscarried February 22, 1926 followed by curettage but there was no period until June 5, 1926. The last period occurred on October 5, 1926. The patient gained weight and noticed a marked growth of hair on the face and abdomen. X-ray treatment was administered on May 10, 18 and 25, 1926. She menstruated normally for 9 months following treatment, then became pregnant and on November 18, 1928 gave birth to a normal boy weighing 9½ pounds. She continued to menstruate normally and in November 1933 gave birth to a second normal boy.

The following case represents amenorrhea and sterility probably due to a persistent corpus luteum.

*Case 11.* Mrs. M. N., age 31, was referred for sterility on June 22, 1945. Menstruation began at 14½ and was always irregular. She married at 18½ years and continued to be irregular, menstruation occurring at about 2-3 months intervals. Six years after marriage she became pregnant and gave birth to a normal boy on August 10, 1940. Following this birth there was a period of amenorrhea of 9 months and menstruation was irregular ever since. No pregnancy occurred in spite of treatment. X-ray therapy was given on June 22, 29, and July 6, 1945. She responded well, menstruated on August 10, 1945 and then became pregnant. On May 23, 1946 she gave birth to a normal girl.

In some cases we thought the action was as Stein and Levinthal (27) suggested, a physical rupturing effect on persistent cystic condition of the ovaries which prevented their normal functioning. This effect was also suggested by Rock and his associates (28) who believed the x-ray ruptured mature ovarian cystic follicles which had failed to rupture spontaneously. This is illustrated by the following cases.

*Case 12.* Mrs. F. C., age 27, was referred in March 1941 for sterility. Menstruation began at 13 and was always irregular—about 5 week intervals. Her last period was in January 1941 and the previous one in November 1940. She was married at 24. In November 1940 curettage was performed and she was advised that she had a cystic left ovary. Menstruation was not resumed after the curettage and in spite of medication did not reappear until January 1941. X-ray therapy was administered in the usual manner on March 17, 24 and 31, 1941. Menstruation reappeared and followed regularly until November 1941. On August 16, 1942 she delivered a normal baby girl.

The following case also illustrates the possible rupture of a cystic ovary by x-rays, (and possible action on a simultaneously existing corpus luteum).

*Case 13.* Mrs. B.O'D., age 30, was referred for irregular menstruation and sterility on August 13, 1926. Menstruation began at 14 and was always irregular; the last period occurred on June 2, 1926. Married at 24, pregnancy 1 year later ended in a still birth. She remained sterile in spite of treatment. A previous gynecological examination revealed a left cystic ovary. X-ray treatment was administered in August 1926. Normal regular menstruation followed and on December 7, 1928 she was delivered of a normal baby girl. Subsequently she had 2 additional pregnancies which unfortunately resulted in unexplained miscarriages.

It is well known that any procedure increasing hyperemia of the uterus will induce bleeding. One of the known effects of x-rays on human tissues is this hyperemia reaction. It is presumed that such action takes place in the uterus initiating the menstrual cycle with subsequent normal periodicity. The absence of immediate bleeding following x-ray therapy, tends to cast doubt on this theory of mechanical hyperemia.

There is no doubt that the thyroid plays an important role in normal menstrual physiology. Hypothyroidism has often been found in amenorrheic conditions and in some cases hyperthyroidism is the influencing agent. Hirsch in 1926 reported that in amenorrhea associated with Basedow's Disease a small dose of x-ray therapy to the ovaries restored menstrual function.

The following case suggests a reaction through the thyroid.

*Case 14.* Mrs. S. F., aged 28, was referred for painful menstruation on April 13, 1931. Menstruation began at 14 and always irregular and painful. She married at 25. There was a large thyroid. She had marked breast swelling at each period. Although she did not practice contraception she did not conceive. Ordinary medical measures proved of no avail and x-ray therapy was suggested. Treatment was administered to the ovaries, pituitary and thyroid. She responded well and gave birth to a baby boy on March 26, 1932. On June 1935 a second boy was born.

Does x-ray therapy stimulate the ovaries? Is it more effective than endocrine therapy? Mazer and Andrussier assert that organotherapy is far less effective than irradiation of the endocrine glands in the successful re-establishment of menstrual periodicity. Frank definitely states that no useful purpose is served by prescribing estrogens for amenorrhea. Rubin (29) also notes the failure of endocrine therapy for amenorrhea and sterility. After ten years of observational cases treated by all types of medication, he found such therapy of little value; on the other hand irradiation yielded results in a large number of cases.

According to Mazer, Israel and Kader, x-ray irradiation perhaps inhibits overaction of the ovarian hormone stimulus and stimulates the corpus luteum secretory action, thereby promoting proper ovulation and affording relief of sterility. Taylor (30) has also shown that organotherapy is of little value in controlling mastitis associated with menstrual disorders, and states that x-ray therapy is often of definite therapeutic value in this condition, achieving their result through the endocrine system. Martius (31) states that any change in the living reactions of the cell is a stimulation response and quotes Flatau as saying that x-rays directly stimulate the ovary. Seitz and Wintz (32) also declare x-rays stimulate ovarian action. Colwell and Russ (33) have shown that x-rays act directly on the follicular elements of the ovaries. On the other hand Lenk (32) says that while the x-rays act on the ovaries by eliminating a pathologic Graafian follicle, the presence of which prevents the ripening of normal follicles, he does not believe the action has a direct stimulating effect on the ovaries.

Rubin, Taylor and others believe that irradiation as used for amenorrhea and sterility acts through a stimulating effect on the ovaries.

Apparently in some instances this stimulating effect on the ovaries alone produced results, and the following cases suggest that the results were due to such action by the x-rays, which were administered solely to the ovaries.

*Case 15.* Mrs. M. B., age 24, was referred for irregular menstruation and sterility on October 10, 1927. Menstruation began at 16, was always irregular, 3-4 months. The last period was on July 4, 1927. She married at 20 following which there was no menstrual change nor did she conceive. Because all other treatment failed she was referred for x-ray therapy. Treatment was given only to the anterior and posterior ovarian areas on October 10 and 17, 1927. She responded well, menstruated regularly for 2 months, became pregnant and in August 1928 gave birth to a normal baby girl. Subsequently she became pregnant again but induced an abortion in May 1929. In January 1936 she again induced an abortion.

*Case 16.* Mrs. G. F., age 29, was referred for sterility on April 8, 1927. Menstruation began at 13 and was always irregular, 3-9 months. Her last period was in February 1927. She was married at 26 but no improvement followed. X-ray therapy was administered only to the ovaries on April 8, 15 and 22, 1927, following which she menstruated regularly for 2 months, became pregnant and was delivered of a normal baby boy on March 15, 1928.

*Case 17.* Mrs. F. S., age 24, was referred for sterility on November 3, 1926. Menstruation began at 13, was regular for years then gradually became irregular and she bled but 3-4 times per year. She married at 22 but no improvement followed. Treatment was ineffective and x-ray therapy was advised. Examination revealed a moderately undeveloped uterus. X-ray treatment was administered to the ovaries on November 4, 9 and 15, 1926. She menstruated, later became pregnant and on August 2, 1927 gave birth to a normal baby boy.

The following case suggests a stimulating effect on the ovaries and the pituitary.

*Case 18.* Age 23, was referred for irregular menstruation and sterility on February 6, 1942. Menstruation began at 11 and was always irregular. She married at 21 and the last period was on January 24, 1942, but the one previous occurred 6 months before on July 24, 1941. She was a well built healthy woman of diminished libido. Other treatment having failed, x-ray therapy was administered to the ovaries and pituitary on February 6, 13 and 20, 1942. Regular menstruation followed, she became pregnant and on January 30, 1943 gave birth to a normal baby girl.

Another case of similar character is the following:

*Case 19.* Mrs. V. J., age 25, was referred for sterility on November 29, 1943. Menstruation began at 13 but was always irregular every 2-3 months. She married at 22 and the last period had just been completed. Many injections were continued after marriage, with no success. X-ray treatment was administered to the ovaries and pituitary on November 29, December 6, and 13, 1943. She responded well, menstruated regularly and on March 1945 gave birth to a normal baby girl.

In some cases where amenorrhea existed while the patient was unmarried, menstruation was restored and subsequent marriage was fruitful following x-ray therapy to the ovaries and pituitary. The following case represents such a course.

*Case 20.* Mrs. M. M., age 21, was referred to me on May 13, 1929, suffering from periods of amenorrhea and severe dysmenorrhea. Varied treatment failed to regulate the periods or relieve the distress. Menstruation began at 11 and was always irregular—at about 3 months intervals. Following x-ray treatment to the ovaries and pituitary, menstruation became regular and was without pain. In 1931 she married and continued to menstruate regularly, became pregnant and gave birth to a normal baby boy on August 4, 1932. On

February 7, 1934 she gave birth to a second boy. She continued to function normally and in September 1936 had an ectopic pregnancy. She now functions regularly.

The case of a single girl treated for amenorrhea who subsequently married and gave birth to a normal baby follows.

*Case 21.* Mrs. S. G. (Miss T. J.) was referred to me when 22 years old for amenorrhea of 1½ years' duration, on August 4, 1942. Menstruation began at 13, was regular until 19, then suddenly ceased following a "nervous breakdown." Medical treatment of all types failed to bring on menstruation and she was referred for x-ray treatment. Therapy was administered on August 4, 11, and 18, 1942. She responded well. She married in November 1942 and menstruated fairly regularly. Then her husband was inducted into the Army where he served for 2 years. Until his return in May 1944 she menstruated regularly until January 1945, became pregnant and on November 2, 1945 gave birth to a normal baby girl.

What part previous pregnancies play in the response to irradiation is still undetermined. Of the 301 married women treated in this series 95 had previously been pregnant. Of this group 34 had miscarried, several more than once, 16 had abortions, 7 had still births, 3 had children who died immediately after birth, 1 had an ectopic pregnancy and 34 had given birth to one or more living children before the present amenorrhea or sterility had appeared.

In my series of 90 women who responded to irradiation with the birth of normal children 16 belonged to the above group. One other case who previous to irradiation had miscarried, became pregnant twice following irradiation and miscarried both times.

The previous pregnancies in this group of 16 resulted in the following: 6 had borne living children, but one of these had also miscarried, 7 had miscarried, 2 had stillbirths, and 1 had an abortion.

Wolf (35) investigating endometrial biopsies obtained from patients with amenorrhea, states that the symptoms may be the result of three possible causes: (1) absence of function of the anterior pituitary lobe, where the gonadotropic hormones originate. (2) Excessive amount of follicle-stimulating hormone, producing single or multiple granulosa cysts in the ovary without corpus luteum formation. The endometrium is hyperplastic (polynormal amenorrhea of Zondek). (3) Excess luteinizing gonadotropic hormone, which results in persistent cystic corpus luteum of the ovary. The endometrium is in the premenstrual phase.

Whether roentgen irradiation directly affects the ovaries, the uterus or the pituitary or is an indefinite stimulant of endocrinologic factors is debatable. The fact remains that it has definitely proved valuable in my hands in the treatment of the cases reported here. No other treatment so far devised, including organotherapy, has yielded equally satisfactory results.

Before x-ray therapy was administered it was determined whether or not the husband was potent for, as Kleegman (36) stressed, the importance of examining the male before treating the female for sterility is evident. In a number of my cases curettage had previously been carried out without relief of symptoms.

All treatments in this series were carried out with high voltage x-rays delivered to the ovaries and in most instances to the pituitary as well. In a few instances the thyroid was also irradiated. As a rule only one series of three treatments

over a three week period was administered, and results usually followed shortly thereafter. In some instances the effect was delayed. In some, the effect continued through several pregnancies. The following case is of interest for it tends to demonstrate the lasting effect of x-ray treatment.

*Case 22.* Mrs. S. M., age 27, referred for sterilization August 16, 1943. Menstruation began late at 19 and was always irregular. She married at 23 but could not conceive in spite of medical assistance. X-ray treatment was administered on August 16, 23 and 30, 1943. Normal menstruation followed and she became pregnant in November 1943 but miscarried in February 1944. She again menstruated normally and on August 20, 1945 gave birth to a baby girl.

As a rule only one series of treatments was given. However in 2 instances this rule was not adhered to, because of the insistence of the patients, who previously had been relieved by x-ray treatment and again demanded relief when they ceased to function normally a second time. The following cases illustrate the result of repeated treatment.

*Case 23.* Mrs. D. O., aged 23, first came to me on September 28, 1938. Menstruation began at 11 but appeared only once or twice a year. She had medical care without result. There was no change after marriage at 21. Further medical treatment was without result. She was of heavy build with much hair over the limbs and pelvis. X-ray treatment was administered September 29, October 6 and 13, 1938. She responded well, became pregnant and was delivered of a normal baby girl August 7, 1939. She menstruated normally for 1 year following the birth of the baby, then became irregular every 3-4 months and the last period was in November 1944. On January 9, 1945 she requested x-ray treatment in order to have another child. I was loathe again to administer x-ray treatment, but the patient was insistent and when the Rubin test proved the tubes to be patent, treatment was administered. One treatment was given on January 9, 1945 and then because no result was achieved treatment was again given in the regular manner on April 13, 20 and 27, 1945. She responded immediately, became pregnant and was delivered of a normal baby girl on December 11, 1945.

In the following case a third series of treatments was administered.

*Case 24.* Mrs. A. S., age 28, came to see me on October 24, 1940. Menstruation began at 13 and was irregular. She was married at 25 and had 1 child after which menstruation ceased. Medication was unavailing. X-ray treatment was administered October 24, 31 and November 7, 1940. The result was good and she was delivered of a normal baby girl, born May 5, 1942, but it was followed by cessation of menstruation. In October 1943 she again requested treatment and after much persuasion I again administered x-ray therapy. Treatment was given on October 18, 25 and November 1, 1943. The patient responded well and was delivered of a normal baby boy on March 10, 1945. Again menstruation stopped completely. In September 1945 she again requested therapy. I was extremely interested in this case to see whether radiation would be effective again. Accordingly x-ray treatment was administered on September 21, 28 and October 5, 1945. Menstruation followed but unfortunately on December 7, 1945 she was stricken with anterior poliomyelitis and menstruation ceased. On March 26, 1946 she notified me that menstruation had recurred on March 22, 1946 and was normal.

I am not yet able to determine what effect the length of sterility has on the response to irradiation. The period of sterility for which relief was sought



in my series of cases varied from a few months to many years. The following cases are examples of longstanding sterility which responded to x-ray therapy.

*Case 25.* Mrs. L. S., aged 33, was referred for irregular menstruation and sterility on January 13, 1925. She was married at the age of 15 but menstruation began at 18 and was always irregular. Unable to conceive, she was referred for x-ray therapy. Treatment was administered on January 13, 21 and 30, 1925. She responded well, became pregnant and gave birth to a baby boy on March 19, 1926, and subsequently a baby girl on March 7, 1928 and another boy on April 13, 1930. On February 3, 1931 she miscarried but has menstruated normally since then.

The following case represents a 5 year sterility period.

*Case 26.* Mrs. B. J., age 30, was referred on July 8, 1927, for amenorrhea and sterility. Menstruation began at 16, but she had only 2 periods and then none again for 14 years. She married at 25 but no menstruation followed. As a child she had scarlet fever, mastoiditis, mumps and measles. All treatment for amenorrhea and sterility failed and x-ray therapy was suggested as a last resort. Treatment was given to the ovaries and pituitary on July 8, 14 and 21, 1927. She responded well with mild menstruation in November 1927 and in August 1928 and irregularly thereafter until the fall of 1930 when she became pregnant. In June 1931 she was delivered of a still born child. She again became pregnant in late 1932 and in October 1933 gave birth to a normal healthy boy. She again became pregnant in 1934 and in October 1935 she gave birth to a baby who died in 4 days.

The following represents a case of 9 years sterility.

*Case 27.* Mrs. E. L., age 27, was referred for sterility on September 17, 1935. Menstruation began at 12 and was regular until 1930, when menstruation occurred only 2-3 times per year. The last period was in February 1935. She married at 18 but was unable to conceive. She was thin and nervous and as the wife of a physician had had numerous treatments. She was a veritable pin-cushion from the many injections she received. X-ray therapy was administered on September 17, 24 and October 1 and 31, 1935, to the ovaries and pituitary areas. Menstruation followed in November and continued normally until May 1936. On February 3, 1937 she gave birth to a normal baby girl.

The following case was sterile for nine years.

*Case 28.* Mrs. K. N., aged 30, was referred on January 22, 1945 for sterility. Menstruation began at 17 and was always irregular, about twice per year and occasionally none for 2 years. She sought treatment but was not relieved. She married at 21 but no change occurred. Treatment was without results. She gained weight and had considerable hair on her body. X-ray therapy was given only once on January 22, 1945 to the ovaries and the pituitary. She responded well and became pregnant in the summer of 1945 and on March 6, 1946 gave birth to a normal baby boy.

The following represents a case of 6 years sterility.

*Case 29.* Mrs. R. W., aged 29, referred for irregular menstruation and sterility on September 1, 1942. She menstruated at 10-11 years of age, always irregular—once or twice a year. She married at 23 but there was no change in menstrual character. In 1941 she had a curettage without favorable result. X-ray therapy was advised and administered on September 1, 8 and 15, 1942. She responded well and menstruated normally for several months became pregnant and on September 22, 1943 gave birth to a normal baby girl.

Another example of a 13 year sterility relieved only after irradiation.

*Case 30.* Mrs. E. R., age 33, was referred for irregular menstruation and sterility on January 24, 1944. Menstruation began at 13, was always irregular—3 to 6 times per year. Her last period occurred on January 11, 1944. She married at 20 and for 13 years remained sterile. Her husband was tested and found normal. After all other treatment failed, she was referred for x-ray therapy. Treatment was administered to the ovaries and pituitary on January 24, 31 and February 7, 1944. She responded well and became pregnant in June 1945 and gave birth to a normal baby boy on April 3, 1945.

There has been marked disagreement on the question of transmission to subsequent generations of injuries alleged to have been produced by roentgen and radium irradiation. According to some authors, the changes in inherited biologic characteristics produced by irradiation are in the mutations, which are markedly increased by irradiation of the genital glands. They quite correctly state that not all the genetic effects of irradiation of experimental animals can yet be translated to humans, for the period of observation in humans has not been long enough. Consequently, if a normal child is born of an irradiated mother, they hold that one cannot conclude that the possibility of injury to the hereditary factor has been eliminated. As to what is termed the safe or tolerance dosage this is merely determined by analogy from results obtained in lower animals and is not based on actual study of humans.

In an effort to evaluate the effects of irradiation of the reproductive organs, these investigators worked with rodents, recording eugenic malformations and transmission of phases of irregular tendencies to progeny by animal parents to whom irradiation had been administered. They maintain that such inherent malformation produced in the genes resulted in abnormal progeny in successive generations of rodents. Their contention that progeny of human beings previously irradiated by even small doses of x-ray would transmit to their subsequent progeny malformations or improper development in structure or organs is based on these observations. It should not be forgotten, however, that while thus presuming to speak authoritatively, the basis for their belief is laboratory experience predicated on the effects on rodents and that they have no actual knowledge based on human beings, for they admit that not enough time has elapsed for observation of the second generation borne of mothers who have been irradiated. In this respect, I hope soon to have a second generation baby upon whom I can report. I refer to a girl born in 1925 to C. A., a patient treated and reported upon by me in my original series of 1931, was married in March 1945. Since puberty she has menstruated normally and is a fully developed young woman. As soon as offspring is reported from this marriage, being the earliest young mother in my series, I shall report its occurrence. Then and only then can we properly determine the effect of x-ray therapy on the progeny of humans treated by irradiation.

In our study of the treatment of amenorrhea and sterility we have seen many children borne of irradiated mothers, and, save in one instance, these children have been normal in every way. The one abnormality was reported by me in 1932 (37) and the reason for this occurrence fully discussed. This abnormality developed after treatment was administered, unknowingly at the time, to a

woman already pregnant. Furthermore, there are numerous reports of normal children born following attempts at sterilization of the mother. Following a period of complete cessation of ovarian function after irradiation applied for sterilization, some women resumed menstrual function, became pregnant and delivered perfectly normal children. In a girl (38) to whom intensive irradiation had been administered by me many years before puberty for a pelvic new growth, with seemingly total sterilization, normal menstrual function was established when she reached puberty and continued normally thereafter.

Another young woman (39) treated by me for puberal bleeding subsequently married and gave birth to two normal children. It is our firm conviction that the effects of irradiation on rodents cannot yet be assumed to apply similarly to humans. Nor have we found any reason to withdraw our repeated opinion that proper therapeutic irradiation for amenorrhea and sterility is harmless and that children borne of mothers so irradiated are in no respect abnormal either physically or mentally.

Treatment in all cases has been with high voltage x-rays, the factors being 200 KV, 5-10 ma with 0.5 mm Cu plus 1 mm Al filter. The earlier cases were treated at a target distance of 30-40 cm., but for some time a target distance of 50 cm. was used. Treatment was directed through the anterior and posterior right and left pelvic fields with 9x12 cm. to 12x15 cm. portals and to the pituitary area through a 6x8 cm. field. The dose was 50 r (measured in air) to the anterior right and left ovarian field and 75 r to the anterior pituitary field for the first treatment. The second treatment was 75 r to the posterior right and left ovarian areas and 75 r to the anterior pituitary field. The third and last treatment was 50 r to the anterior right and left ovarian areas and 75 r to the anterior pituitary area. Occasionally a fourth treatment was given. In the early series only the ovaries were treated; at present each time the pelvis is treated the pituitary is also treated.

Whether or not age is a determining factor is still a moot question. There is no doubt that the younger the women the more probable the relief of sterility, yet we noted some definite results even in older women. The youngest single girl treated was 16 and the oldest 30 years of age. Among the married seeking relief, the youngest was 18 and the oldest 45. The largest number of married women were in the 27-30 year age group, and 111 of the 305 married women were in this group.

The successfully married cases were in the 21-39 year group. They were distributed as shown in Table I and II.

The following case although in the older age group responded well to treatment and gave birth to normal babies.

*Case 31.* Mrs. M. S., age 34, was referred for sterility of 8½ years duration on March 11, 1942. Menstruation began at 11 and was always irregular. The last period had just been completed. She married at 25 and was anxious to have children. She was extremely nervous. X-ray treatment was administered on March 11, 18 and 25, 1942. She responded well and on December 28, 1943 gave birth to a normal baby boy.

*Case 32.* Mrs. A. H., age 32, referred to me on July 24, 1941 for sterility, of 5 years dura-

tion. Menstruation began at 13, and was regular. She married at 27 and for 5 years in spite of medical attention failed to become pregnant. X-ray treatment was administered on July 24, 31 and August 7, 1941. She responded well and gave birth to a baby girl on March 9, 1945.

TABLE I  
*Ages of Patients*

NO. OF PATIENTS	AGE OF PATIENTS	NO. OF PATIENTS	AGE OF PATIENTS
2	16	34	30
2	17	21	31
4	18	18	32
5	19	20	33
3	20	15	34
11	21	9	35
14	22	4	36
20	23	5	37
23	24	3	38
18	25	6	39
17	26	3	40
29	27	3	42
30	28	2	45
18	29		

TABLE II

NO. OF PATIENTS	AGE OF PATIENTS
6	21
6	22
6	23
9	24
4	25
7	26
12	27
9	28
6	29
9	30
4	31
6	32
3	33
3	34

In some cases although x-ray therapy evidently does correct the functional amenorrhea and promotes fertility the woman fails to carry through a normal pregnancy. I am at a loss to account for such failures. In the normal course of pregnancy there are also a number who spontaneously miscarry. Perhaps the miscarriages in my series fall into such idiopathic groups. For example in the following case although x-ray treatment was successful and pregnancy occurred the patient subsequently miscarried, perhaps due to her age.

*Case 33.* Mrs. W. M., was referred to me in July 1945, for treatment for sterility. She was 39 years old. Menstruation began at 14 and was always regular. She was married at 31 but never became pregnant and was anxious for a child. She had endometrial biopsies, tubal inflation and a long series of medications without results. Following x-ray treatment on July 6, 13 and 20, 1945 she continued to menstruate regularly until October 1945 when she became pregnant. However, she miscarried in December 1945 without apparent reason except perhaps the excess athletic activity or maybe because of her 39 years.

The following case is of interest because of the patient's inability to carry the pregnancy which successfully followed x-ray therapy.

*Case 34.* Mrs. L. S., aged 24, was referred for sterility treatment on November 13, 20, 27, 1941. She responded well to treatment, became pregnant but miscarried in August 1942. Again she menstruated normally and became pregnant in February 1945 but unfortunately in September 1945 again spontaneously miscarried. I am unable to explain this phenomenon.

The following case is of interest because of the favorable response to irradiation and of the subsequent abnormal pregnancy.

*Case 35.* Mrs. M. R., aged 31, was referred to me on May 5, 1942 for sterility. Menstruation began at 18 and was always regular. She had had an illegitimate pregnancy in 1936 with an induced abortion but continued to menstruate normally thereafter. In 1940 she miscarried at the age of 29 but subsequently continued to menstruate normally. Artificial insemination was attempted without success. As a last resort she was referred for x-ray therapy. Treatment was administered to the pituitary and ovaries on May 5, 12 and 19, 1942. She menstruated normally and later in 1944 became pregnant but this proved to be an ectopic pregnancy. I am not sure whether age alone was the determining factor for the failure to bear normally in this case.

No patient ever comes directly to the Radiation Therapist for x-ray treatment for sterility. Practically every case is referred by a gynecologist because every other available treatment has been unsuccessfully tried. The indication for x-ray therapy is simple. Any woman who desires a baby, and who has failed to respond to other therapeutic measures should have a trial with irradiation. The younger the woman the better the chance of success.

The most common symptom for which patients were referred for irradiation was amenorrhea, which varied in duration from a month to several years. In some cases which were referred for sterility treatment, menstruation had been regular yet no pregnancy occurred. In some cases menstruation was reported scanty. There was no appreciable difference in responsiveness in either type of menstrual dyscrasia, those with regular, scanty or irregular menstruation appeared to react no differently than those who suffered complete amenorrhea. As yet, I have no way of determining before treatment which cases will respond. At present, I am inclined to agree with Rubin and Taylor that x-ray therapy has, in some way as yet not explained, a general stimulating action, resulting in the relief of amenorrhea and sterility in a large number of cases. The following cases are examples of what I believe suggests a general stimulation effect of the x-rays.

*Case 36.* Mrs. C. A., aged 28, was referred for dysmenorrhea and sterility on June 9, 1925. She menstruated at 11, was always irregular and always suffered severe pain with the



periods. She married at 26 but no relief followed. The last period was in May 1925. Because other methods of treatment failed she was referred for x-ray treatments, which was only administered to the ovarian areas on June 9, 16 and 30, 1925. Regular painless menstruation followed treatment, she became pregnant and was delivered of a normal girl baby in January 1927.

*Case 37.* Mrs. Y. C., age 26, was referred for sterility on April 20, 1930. Menstruation began at 15 was never quite regular. She married at 20 and continued irregular. The last period occurred on March 15, 1930. Not becoming pregnant she resorted to medical aid for 6 years without result. X-ray therapy was recommended and was administered to the ovaries and pituitary April 21, 28 and May 5, 1930. Normal menstruation followed treatment, she became pregnant and on May 8, 1931 was delivered of a normal baby girl.

*Case 38.* Mrs. P. B., age 33, was referred for sterility on November 15, 1937. She began to menstruate at 13 always regularly. She was married at 20 but for 13 years did not conceive. The last period was on October 29, 1937. She had had numerous treatments to no avail. She was referred for x-ray treatment which was administered to the ovaries and pituitary on November 15, 22, and 29, 1937. She responded well, became pregnant and gave birth to a normal baby boy on August 3, 1940.

*Case 39.* Mrs. L. L., age 22, was referred for irregular menstruation and sterility on December 22, 1937. Menstruation began at 12 and was always irregular. She was married at 19. There was no improvement. The last period was on November 30, 1937. When all other treatment failed, irradiation was administered on December 22, 29, 1937 and January 5, 1938 to the anterior and posterior ovarian and anterior pituitary areas. The patient responded well and menstruated regularly until December 1938 when she became pregnant and was delivered of a normal baby girl on September 22, 1939.

*Case 40.* Mrs. F. T., age 30, was referred on August 1, 1938 for irregular menstruation and sterility of 5 years duration. Menstruation began at 13 and was always irregular. She married at 25 and her last period occurred on June 1938. All other treatment having proven unavailing she was advised to have x-ray therapy and this was administered on August 1, 8, and 15, 1938 to the ovarian and pituitary areas. Regular menstruation followed until November 1938 when she became pregnant and on August 2, 1939 was delivered of a normal baby boy.

*Case 41.* Mrs. R. Z., age 23, was referred for amenorrhea on August 13, 1942. Menstruation began at 12 and was always irregular. She married at 20½. The last period had just been completed. Other treatment proved unavailing and x-ray therapy was administered on August 13, 20, and 27, 1942. She responded well, became pregnant and on December 29, 1943 gave birth to a normal baby boy.

*Case 42.* Mrs. R. S., age 27, referred for amenorrhea on January 13, 1943. She menstruated at 13½ and was regular until the last period in September 1942. She married at 24½ and believed she had a "false" pregnancy in March 1942. However, she menstruated in September 1942, but not since. Curettage and medication failed to correct the condition and she was referred for x-ray therapy. Treatment was administered on January 13, 20 and 27, 1943 to the ovaries and pituitary. She responded well, became pregnant and gave birth to a normal baby boy on September 3, 1944.

Another question which still remains unsolved is that concerning the failure of women to conceive in whom normal menstruation has been restored following irradiation.

In most instances, during the period of amenorrhea, the woman fails to become pregnant, but soon after menstrual regularity is restored she may conceive and bear children. In many of my cases such a sequence followed x-ray treatment. However, in some cases although the menstrual function had been reestablished and occurred regularly after treatment, no pregnancy followed. Just why, I am as yet unable to say. Perhaps such women are naturally anov-

ulatory in spite of restoration of monthly bleeding. The reason for this paradoxical action following x-ray therapy is still being sought.

The following cases are a few examples of those who responded to irradiation after periods of amenorrhea but who did not conceive in spite of regulation of the menstrual cycle.

*Case 43.* Mrs. E. A., age 31, was referred for amenorrhea and sterility on May 28, 1946. Menstruation began at 13 and was regular until she was 18. Then for no discoverable reason she bled but 2 times per year. She married at 26 and the last menstruation occurred in September 1945. X-ray treatment was administered to the ovaries and pituitary on May 28, June 4 and 11, 1946. Normal menstruation followed and she has continued to menstruate normally every month (up to October 1946) but has failed to conceive.

*Case 44.* Mrs. L. B., age 34, was referred for sterility on October 30, 1945. Menstruation began at 13½ and was always scanty. She married at 22 and the last menstruation was in March 1945. She has one child and had 3 miscarriages but was anxious to have one more child. X-ray treatment was administered to the ovaries and pituitary on October 30, November 6 and 13, 1945. She responded well and has menstruated regularly since then but has failed to conceive.

*Case 45.* Mrs. E. A. C., age 33, was referred for amenorrhea on July 18, 1938. Menstruation began at 15, at first regular but gradually became irregular and for 2 years, since September 1936 had no menstruation. Medical care proved of no help. She married at 32 but no improvement followed. X-ray therapy was advised and administered to the ovaries and pituitary on July 18, 25 and August 1, 1938. Following treatment she menstruated regularly but up to the present time has not become pregnant.

*Case 46.* Mrs. R. D., age 26, was referred for amenorrhea on March 19, 1945. Menstruation began at 11½ and was always irregular every 8 or 9 months. Medical treatment was constantly given without result. She married at 20 but there was no improvement. The last period occurred on January 28, 1945. X-ray treatment was administered on March 19, 26 and April 2, 1945. Regular menstruation followed but as yet she has failed to become pregnant.

The only contraindications to irradiation are: the absence of/or destruction of the generative organs, or tube closure. Irradiation is not indicated where sterility is due to impotency of the husband.

Where menstruation ceases entirely after this type of stimulating x-ray the cessation is not due to the irradiation but occurs in spite of it. Such menopause action would have occurred in a short time regardless of treatment. Of course irradiation is contraindicated in the presence of pregnancy.

Over the course of 20 years a total of 301 married women were treated by x-ray therapy for amenorrhea and sterility. Of these 70 were not traced, 55 failed to respond to treatment and 171 had menstruation regulated. Of the latter, 90 became pregnant; 77 went to term, 20 more than once and gave birth to 102 normal children, (45 boys and 57 girls) and there was 1 set of twin girls.

*Case 47.* Mrs. I. G., age 30, referred for amenorrhea and sterility on September 17, 1926. Menstruation began at 12 and was regular until she was 22 years old, when irregularity began with long periods of metrorrhagia. She married in 1923 at 27 years of age and the last period, which was scanty, occurred on May 16, 1926. She had become pregnant shortly after marriage but miscarried in September 1924. She bled again in November 1924, January, February, July and October 1925 and then not until May 1926. Gynecologic examination revealed no pelvic abnormality. Other treatment proved unavailing and x-ray therapy was advised. Treatment was administered to the ovarian and pituitary

areas on September 17, 22 and 27, 1926. She responded well, menstruated normally for 4 months, became pregnant and in November 1927 gave birth to normal twin girls.

There were 32 pregnancies following irradiation but without living children. Of these 18 miscarried, several a number of times, 2 were ectopics, 1 had a still birth, 3 had normal births but the children died a few hours after birth, 6 aborted and 1 had an abnormal child. There are 5 cases still pregnant and 1 case was therapeutically aborted. Two cases were retreated and gave birth to a second child. Two women who did not respond adopted babies and one of these is now pregnant.

The case which was therapeutically aborted evidently was pregnant when treatment was begun and as soon as this fact was noted the 5 week pregnancy was interrupted because I could not assure the parents-to-be of a normal child. In this case of incipient pregnancy I was not sure that even the small dose used for stimulation might not have been of sufficient potency to damage the very early embryo, and because of the one case of abnormality previously reported by me in 1932, I deemed it advisable to interrupt the pregnancy.

#### CONCLUSION

Because of the successful results secured through irradiation in the large number of cases in this series, with subsequent follow-up of children born of irradiated mothers, I feel warranted in reiterating my previous conclusions that irradiation when properly given, is harmful neither to the mother nor to the offspring and that it has proved to be a valuable therapeutic procedure for the treatment of amenorrhea and the relief of sterility.

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## SOME RECENT BIOLOGIC INVESTIGATIONS AND THEIR SIGNIFICANCE FOR PATHOLOGY

PAUL KLEMPERER, M.D.

(New York, N. Y.)

*From the Laboratories, Division of Pathology, The Mount Sinai Hospital, New York*

Pathology as a branch of natural science is concerned with the inquiry into the immanent reason of disease. The pathologist investigates manifestations of life under morbid conditions, while the biologist applies himself to an analysis of the various aspects of normal life. Obviously, methods which have proven their value in biologic investigations must be of great interest to pathology. Reference to manifestations of disease can be found in the oldest records of the history of mankind. A magnificent system of empirical knowledge of symptoms and symptom complexes, mainly of functional nature, has been transmitted to posterity in the works of Hippocrates and the medical writers of antiquity. One must admire their keen and exact observations, and it is a source of inspiration to appraise the intuition by which they divined correlations which modern medicine is just beginning to establish [Petersen, W. F. (1)]. "Genius is revealed," says Claude Bernard (2), "in a delicate feeling which correctly foresees the laws of natural phenomena." Yet the observations and doctrines of Hippocrates and Galen are today only of historical interest. Modern medicine has been founded upon systematic and rational inquiry into the nature and cause of disease. It was primarily based upon the premise that the clinical evidences of disease must be correlated with alterations in the structure of organs and tissues.

This doctrine [Der anatomische Gedanke Virchow (3)] established by Morgagni and subsequently advanced by the French and English school of brilliant clinician-pathologists achieved its greatest triumph in Vienna through Rokitansky. There, under his leadership, clinicians learned to correlate the variable clinical symptoms of disease with the finality of altered structure. Pathologic anatomy became the foundation of diagnostic reasoning in medicine. But amidst the enthusiastic believers who saw alterations of structure as the only pivot of the problem of disease there were a few cautious voices who warned against overestimation. Jacob Henle (4), one of the finest minds of the nineteenth century anatomists and pathologists, wrote in his Handbook of Rational Pathology about the mere substitution of perceptible anatomic lesions for empirical clinical symptoms. He pointed out that structural alteration was a manifestation only but not the reason of disease. Bretonneau (5), who first identified the lesions of typhoid fever and diphtheria spoke skeptically about the absolute value of morbid anatomy in comprehending the nature of disease.

Today one can hardly appreciate the significance of these objections because the etiologic viewpoint and the striking advance of functional research in medicine have shown the inadequacy of a narrow anatomic dogma concerned only



with structural alteration in disease. But in that period medical thought had just found a firm foundation upon which to anchor the shifting symptoms of disease. Morgagni and those who followed him firmly believed that *seat* as well as *cause* of disease was revealed by anatomic investigation. It required discrimination and courage to oppose a doctrine which seemed to offer a rational answer to all the puzzling questions which had vexed generations of physicians for centuries.

But the overestimation of the structural concept, the objective characterization of disease, could not satisfy medical philosophy for long. A generation which was witnessing the advances of chemistry and physics and which had been convinced of the causality of natural phenomena, could not rest content with the static propositions of morbid anatomy.

Rudolf Virchow is respected as a great anatomist; his cellular pathology has been regarded by some as a mere refinement of gross pathology. Virchow was indeed a representative of anatomic thought in medicine. He proclaimed in his *Cellular Pathology* (6) "that at all times permanent advances in medicine have been distinguished by anatomic disclosures, that every major epoch has been initiated by a series of important discoveries of the structure and fabric of the human body." But he realized that the perception of morbid lesion was not the ultimate object of pathology, that structural alteration was not the immanent reason of disease. "The fundamental error (sc. of a narrow morphologic concept of disease) lies in the confusion of the anatomic with the material." "We also," he continues, "cannot conceive of any phenomenon of life, however functional it may appear, without an alteration of matter; but need it be anatomic, can it not be chemical?" With these words written in 1854, Virchow (7) defined the aim of pathologic inquiry. And a few years later he gave a precise directive for future research. In a lecture (8) before the German physicians and natural scientists he stated: "By calling attention to the cell I desired to provoke investigators to inquire into the processes within the cell, to define that what happens within these smallest elementary organisms. And it was self-evident that an exact definition could be nothing else than to find the chemical and physical foundations upon which vital phenomena and the activity of the cell are based."

Today, eighty years after this challenge was sounded, we morphologic pathologists are still concerned with the anatomic, structural niceties of tissues in disease, and relegate to the test tube the fundamental inquiry into the nature of the living substances. Yet we need no longer be limited to investigations of organ or tissue extracts only. Tools are ready and methods available by which we can investigate the chemical composition of organic matter within the cell or its formed partitions.

Modern cytology has made remarkable advances by separating the ultra-structures of nucleus and cytoplasm and identifying their chemical constitution and vital activity. One of the most fascinating aspects in recent years has been that of the significance of the nucleic acids in the economy of the cell. From the investigations of geneticists, cytologists, enzyme chemists and physicists it can be concluded that the nucleic acids play an important role in the mechanism

of heredity, cell division, protein synthesis and enzyme activity of the cell. Nucleic acid of one type, the desoxyribose form, was first chemically isolated by Miescher from the nuclei of leucocytes and spermatides. Its visualization in tissue sections was accomplished by Feulgen (9) whose method is that of mild hydrolysis with dilute hydrochloric acid and subsequent treatment with a sulphurous fuchsin solution. The principle of this staining reaction is the liberation of a free aldehyde group by the mild hydrolysis and its determination by sulphurous fuchsin. This staining procedure is a true chemical reaction and characteristic only for desoxyribonucleic acid. The other form of nucleic acid, ribose nucleic acid, has been found within the nucleolus and cytoplasm of cells, particularly in the vicinity of the nuclear membrane. It has been located by Bensley (10) and his co-workers within the mitochondria, by Claude (11) and associates who used the ultracentrifuge for separation of the ultraparticles of the cytoplasm, within the mitochondria, microsomes and secretory granules. Both nucleic acids have a characteristic absorption spectrum for ultraviolet light and can be detected even in minimal amounts by spectromicrography. With this method Caspersson (12) and associates investigated the minute structure of the nucleus and have brought to light most fundamental facts regarding the organization of chromosomes, genes and nucleolus. They and others [Koller (13), Bieseke (14), Stowell (15)] have also presented interesting evidence pointing to an intracellular disturbance of nucleic acid metabolism in human and experimentally produced carcinoma. Alteration of nuclear and cytoplasmic structure such as large nucleoli, abnormal chromosomes, basophilia of cytoplasm, diagnostic criteria, familiar to every conventionally trained pathologist, can now be interpreted and further investigated as manifestations of a disturbance of chemical processes in living substance. The dynamic significance of these revelations for the tumor problem might be indicated by reference to investigations of geneticists who have shown the deleterious effect of roentgen radiation upon the genes. On the other hand, observations of physicists have demonstrated that nucleic acids are depolymerised by x-rays. It might also be mentioned that the effect of nitrogen mustard upon *Drosophila* chromosomes and tobacco mosaic virus similarly points to an action upon the nucleoproteins [Gilman, A. and Phillips, F. S. (16)].

Another line of histochemical research is concerned with the demonstration of enzymatic activity within tissues. Methods for the visualization of general and specific oxydases have been known for many years and need only be mentioned here. More recently, Takamatsu (17), and simultaneously Gomori (18), devised techniques for the demonstration of alkaline phosphatase within tissue sections. Subsequently, methods were developed by Gomori (19) to disclose the activity of acid phosphatase and lipase. Numerous investigations have established the distribution of these enzymes in the various organs of different species of mammals, including man. Alterations of phosphatase activity in experimentally produced lesions of kidneys and liver have been studied by a number of authors. The literature on the subject is well reviewed in a recent article by M. Wachstein (20) who also adds valuable results of his own investigations including observation on lipase activity. It is interesting that acute renal injury with mercury

bichloride, uranium nitrate and potassium dichromate does not affect the alkaline phosphatase activity. In the regenerating tubular epithelium, however, following the acute necrotising damage caused by the heavy metals, the activity is decreased. In experimental hydronephrosis where tubular damage becomes evident within a few weeks after ureteral ligation, alkaline phosphatase activity is strikingly decreased although the structural damage seems much less severe than in intoxication with heavy metals [Willmer (21)]. Lipase activity shows an identical behavior [Wachstein (20)]. It would lead too far to give more details of the experimental research which has been reported in the past years. Studies on human pathologic material are still fragmentary; it is obvious that investigations on post mortem material must be conducted with great caution, and the accumulation of sufficient unequivocal data is time consuming.

Most recently, Krugelis (22) correlated alkaline phosphatase activity with nucleoproteins within chromosomes, nucleolus and cytoplasm. This is of great significance because the nucleoproteins are themselves naturally occurring phosphate bearing substances. By ingenious methods this author demonstrated the presence of specific nuclear as well as cytoplasmic phosphatases. These investigations may lead to a keener insight into the mechanisms of nucleic acid metabolism and chromosomal activity.

Since the cell was established by Virchow as the center of vital activity in health and disease, anatomic pathologic investigations have been conducted mainly with the aim of disclosing the structural manifestations of disease evident within the cell. But the founder of cellular pathology was not unmindful of the existence of intercellular substances. However, he regarded them as non-living material and was obviously not much concerned with their possible significance in the economy of life. Yet the universal distribution throughout the animal and human body of mesenchyme which consists largely of intercellular substance calls for inquiry into its structure and chemical and physical constitution, especially since its implication in disease has become obvious in recent years. A comparative microscopic analysis of connective tissue in its different locations and in its evolution reveals that its extra-cellular component consists of a homogeneous ground substance and of collagenous fibers. (A consideration of the elastic fibers and the so-called reticulum fibers must be omitted in this presentation.) Investigation of the ground substance with the conventional staining methods of histology is unsatisfactory because of the absence of structural differentiation. Nevertheless there are unmistakable indications both under normal as well as pathologic conditions of differences in density as well as in chemical constitution. The latter becomes apparent upon application of certain staining methods for mucus. While these methods cannot yet be considered as exact chemical tests, they do indicate the presence of certain chemical compounds. Thus, toluidine blue in dilute solution points to mucoproteins with sulphuric acid esters of high molecular weight and a recently devised method reveals the presence of acid polysaccharides. Hyaluronic acid can be determined by the decrease in stain-ability of the ground substance after hyaluronidase has been allowed to act upon the tissue section.

The chemical approach is not the only one for identification of alteration of the

homogeneous ground substance. The obvious differences in its density in pathologic conditions point to possible alterations of its colloid phase. Investigations by Herringa (23) and his associates have shown variability in the capacity for water adsorption of the connective tissue ground substance of the cornea. Drs. Grishman and Sender in our laboratories have found differences in water adsorption of the skin of guinea pigs in experimental scurvy. Application of identical methods in the investigation of human pathologic conditions promises interesting results. Such procedures, however, are not only most complicated, but actually take the anatomist into a field of research which is not germane to his training. He must join forces with the biophysicist who is competent to carry out such investigations. The anatomic pathologist must find his way out of the narrow confines of mere structural definition of morbid alteration and explore the material foundation of changes in form. Lack of optical differentiation must not remain an insurmountable obstacle in his inquiry into the nature of tissue changes in disease. The advances in biophysics, the development of scientific tools such as the electron microscope and x-ray diffraction apparatus, offer the possibility of investigation of the living substance at the level of molecular constitution.

The opportunity and necessity of such an approach is well illustrated by the problem of morbid states with conspicuous implication of the collagenous tissues. The interest of pathologists in the connective tissues of the human body was awakened by Aschoff and subsequent workers because of the obvious and widespread collagen damage observed in rheumatic fever [Klinge (24)]. Investigations of experimental allergy also revealed fundamental affection of collagen fibers. Baehr, Pollack and I (25) were so much impressed by generalized connective tissue alterations in acute lupus erythematosus and scleroderma that we interpreted the apparently heterogeneous and widely disseminated lesions of the heart, vascular system, kidney, skin and serous membranes as manifestations of a fundamental alteration of collagen. The affected connective tissue fibers displayed increased eosinophilia, thickening, straightening and friability evidenced by frequent fragmentation. The interfibrillar ground substance seemed increased in amount and stained distinctly in contrast to its usual appearance when it is hardly visible. These structural aberrations could not be classified with any one of the known categories of general pathology. They could only be regarded as the visual expression of a change in the chemical and physical constitution of the intercellular substance. While these changes were most striking in a certain number of cases, we had to admit that they were less conspicuous and even absent in another group of cases with identical clinical course.

How can one account for such a discrepancy? We believed in 1942 that it was not too fantastic to assume that a derangement of the colloidal, i.e., physical state of the entire collagenous system, could exist, though it cannot consistently be revealed by our conventional histologic method. Accordingly, we suggested that this system should be explored with the methods available to the biophysicist. The application of x-ray diffraction and electron microscopy has already disclosed the molecular structure of collagen fibers [F. O. Schmidt (26)]. It will



be interesting to investigate the ultrastructure of collagen tissue in such diseases in which the examination with the light microscope has brought forward evidence of its fundamental alteration. In the Physics laboratory of our hospital S. Feitelberg has been engaged in investigations of the x-ray diffraction pattern of connective tissue in different age periods with particular reference to the homogenous ground substance.

It is obvious that this brief review of recent biologic investigations can only touch upon the brilliant research of cytologists, geneticists and biophysicists. The application of their discoveries to problems of human pathology has hardly begun. A discussion of their implications for pathology is therefore concerned less with facts than with the vista of future investigations. This seemingly empty speculation of a morphologist might be excused by his solicitude for the unfortunate situation in which pathologic anatomy finds itself today. Pathology concerned with structural alterations has made signal contributions in the past to the knowledge of the nature of disease. Yet in recent years the remarkable success of research mainly concerned with the functional and etiologic aspect of disease has suggested to some that the usefulness of morphologic investigations of morbid states has reached an end.

In the past, anatomic pathologists had to be content with the analysis and identification of structural alterations in disease. But visible structure and ultimate matter are indissolubly connected [Needham (27)]. Inquiry into alterations of matter in disease and interpretation of structure in terms of matter has now become possible. Anatomic pathology has the opportunity to reclaim its leadership.

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# SURGICAL MANAGEMENT OF GASTROJEJUNOCOLIC FISTULA

## A REVIEW OF EIGHT OPERATED CASES

PERCY KLINGENSTEIN, M.D.

(New York, N. Y.)

*From the Surgical Service of Dr. Ralph Colp, The Mount Sinai Hospital, New York*

Gastrojejunocolic fistula following gastroenterostomy is more serious and life threatening than the original lesion for which the procedure is employed. We are excluding from discussion the rare spontaneous communication between stomach and colon caused by carcinomatous or foreign body perforation. In contradistinction, marginal or jejunal ulceration with secondary invasion of the colonic wall and perforation into its lumen is not infrequently seen in all large surgical clinics following posterior gastroenterostomy. In almost all instances the original operation of gastroenterostomy was performed for duodenal ulcer. This corresponds with our own experience. The eight cases furnishing the basis of this study were operated upon originally for duodenal ulcer. Only a very few cases are recorded in which fistula resulted following a short-circuiting procedure for gastric ulcer. Two factors may account for this variance. The acid values in gastric ulcer are notoriously lower than in corresponding lesions of the duodenum. The second factor is the relatively much longer time that gastrectomy has been employed as the procedure of choice in the surgical management of gastric ulcer.

*Incidence.* It is difficult to accurately estimate the frequency of gastrojejunocolic fistula. Ransom (1) reported eight cases with fistula in a series of 47 with marginal or jejunal ulcer operated upon in a ten year period, an incidence of 17 per cent. We have treated a similar number surgically out of a total of 44 with stomal ulceration admitted to the gastric surgical service of the Mount Sinai Hospital during a thirteen year period. None of these complicated by fistula followed subtotal resection of the stomach and it is fair to assume that this dread complication will diminish when gastrectomy is practiced for the cure of duodenal ulcer. It will be appreciated that approximately one patient out of six who develops an anastomotic ulcer is exposed to the added complication of fistula formation. Further evidence that gastrojejunocolic fistula is not uncommon is the relatively large number of cases reported by Judd (2) from the Mayo Clinic and by Marshall (3) from the Lahey Clinic.

*Age and sex.* It is of interest to note that in our own experience all cases occurred in males. This corresponds to the findings of others. In a series of 52 gastrojejunocolic fistulas reported by Judd (2) all were males but one. The youngest in our group was 37, the oldest 69. Three patients were in the fourth, one in the fifth, three in the sixth, and one in the seventh decades of life. The literature records cases of fistula in patients as young as twenty and as old as seventy-two.

*Type of previous operation.* In all our cases a posterior gastroenterostomy had

TABLE I  
*Résumé of Eight Cases of Gastrojejunocolic Fistula*

CASE	AGE	SEX	PREVIOUS OPERATION	TIME INTERVAL BEFORE DEVELOPMENT OF FISTULA	DURATION OF AND PRESENTING SYMPTOMS	X-RAY FINDINGS	OPERATION	PATH REPORT	RESULT
1	52	M	Post gastro-enterostomy	3 yrs.	3 months Liquid bowel movements; belching of fecal tasting gas	Gastro-colic fistula	Preliminary ascending colostomy; subtotal gastrectomy and jejunectomy—colonic fistula healed; closure of colostomy	Chronic peptic ulcer of jejunum	Well
2	57	M	Post gastro-enterostomy	25 yrs.	9 months Watery stools; fecal eructations	Gastro-colic fistula	Ascending colostomy; Excision of fistula with restoration of gastrointestinal continuity; closure of colostomy. One year later subtotal gastrectomy for reactivated duodenal ulcer	Chronic peptic ulcer of duodenum	Well
3	51	M	Post-gastro-enterostomy	30 yrs.	2 years Intractable diarrhea	Barium enters stomach from region of splenic flexure	1 stage operation—re-pair of colonic fistula—subtotal gastrectomy	Stomach showing G.B. stoma with acute and chronic gastritis	Well
4	43*	M	Two posterior gastroenterostomies	12 and 9 yrs.	6 months "Foamy stools" Tetany	Fistula between jejunum and distal transverse colon	Transverse colostomy		Ceased

5	39	M	Post-gastro-enterostomy	18 months	5 months Loss of weight; nocturnal diarrhea. Belching of foul gas	Jejunal ulcer and jejuno-colic fistula	Ascending colostomy, gastrectomy, partial jejunectomy, partial colectomy; closure of ascending and transverse colostomy	Resected stomach, jejunum and colon with large indurated colonic fistula	Well
6	37	M	Post-gastro-enterostomy	12 yrs.	6 months 6-7 watery bowel movements per day	Colonic gastric communication	1 stage gastrectomy, jejunectomy and colorrhaphy	Chronic peptic ulcer of jejunum	Well
7	37	M	Suture of perforation. Subsequent post-gastroenterostomy	10 yrs.	6 months Diarrhea; weight loss; fecal vomitus	Shows gastrojejuno-colic communication	1 stage gastrectomy, jejunectomy and colorrhaphy	Healed erosion of jejunum	Well
8	69	M	Posterior gastro-enterostomy	4 yrs.	6 months Diarrhea, weight loss and emaciation	Gastro-colic communication	Division of fistula; colorrhaphy and jejunorrhaphy; Restoration of gastrointestinal continuity. Subsequent posterior gastro-enterostomy		Well

\* Post mortem jejuno-colic fistula—cause of death inanition; gastric dilatation; pulmonary edema.

previously been done. In one case—the only fatality in this series—a second gastroenterostomy was performed in another hospital for symptoms suggesting marginal ulcer with hemorrhage. No case has been encountered in which partial gastrectomy was the primary procedure. This may be accounted for by the fact that for the past ten years we have been employing an anterior type of gastro-jejunal anastomosis which effectively removes a possible anastomotic ulcer from the intimate relationship to the mesocolon and colon with eventual perforation into the latter.

*Time interval between primary operation and fistula.* This subject poses many interesting problems because of the extreme variance that occurs between the original operation and the development of symptoms referable to the gastrocolonic fistula. In two patients symptoms commenced 27 and 30 years after the gastroenterostomy. The shortest time interval was two years. In the vast majority of cases, symptoms of recurrent ulcer were manifest for a considerable period of time before perforation into the colon was evident.

*Diarrhea.* This symptom was outstanding and the one that influenced the patient to seek surgical therapy. It occurred in all patients. It was surprising to find how long these patients carried on before entering the hospital. The shortest period of diarrhea was of three months duration as opposed to the longest which persisted for two years. The number of bowel movements was variable, usually between six and twenty a day. The consistency and character of the stools varied also. In some they were described as "foamy," in others watery. Efforts to control the diarrhea were for the most part ineffectual. The question of whether the diarrhea is the result of the direct emptying of gastric contents into the colon through the fistula as evidenced by particles of undigested food in the feces or whether it is due to small intestinal irritative hypermotility is of interest. Clinical and x-ray evidence would give some credence to the latter hypothesis. In one patient there was x-ray evidence of only a jejunocolic communication. Diarrhea was nevertheless present.

*Fetid eructations and vomiting.* This symptom was as constant and as disturbing as was the diarrhea in all but one patient. In this case the barium enema showed a fistulous tract between the colon and jejunum without evidences of a direct gastrocolic opening. Vomiting was not as constant a feature. It occurred in two cases and was described as foul and "fecal" in character.

*Pain.* Pain was a very variable and inconstant symptom. A careful history usually elicited the periodic pain of a jejunal ulcer occurring in cycles with exacerbations and improvement especially when treated with bed rest and a strict ulcer regimen. With the onset of diarrhea the pain seemed to abate and on admission to the hospital was not outstanding. It is difficult to understand why this should occur in the presence of a large inflammatory process unless it can be explained on the basis of an absence of penetration into the mesentery of the small bowel which we have found to be persistently associated with pain of the severest character.

*Loss of weight.* This was present in all our cases. The greatest loss in weight was forty pounds in one patient, the least ten pounds. The average loss was



twenty pounds in spite of an unimpaired appetite and a liberal diet in most cases.

#### PHYSICAL FINDINGS

*Local.* The local findings are usually meager. Tenderness on abdominal palpation is found in a small percentage of patients with the maximum point of sensitivity to the left of the umbilicus at a point on the level of the umbilicus. Slight protective abdominal spasm is sometimes found but true abdominal rigidity was not present in any case. No mass could be palpated through the abdominal wall although at operation a tumefaction the size of an orange was present in two cases.

*General.* The patient appears chronically ill. There is evidence of marked weight loss and inanition. The skin is dry and scaly and the normal integumentary elasticity is absent. The facial expression is not unlike that in a patient with acute dysentery. The eyes are sunken and the tongue dry and furred. The tongue is often glazed, cherry red, presenting lingual evidence of a marked degree of vitamin deficiency. Hemoconcentration due to fluid loss masks an anemia which reveals itself upon restoration of fluids. A low grade temperature is not uncommon.

*Laboratory findings.* In the main, gastric secretory studies revealed lower free and total acid values than ordinarily found in primary duodenal ulcer. In one patient there were 80 free and 128 total units of acid present. Blood proteins were uniformly low. In two patients the values were reduced to 4.2 gm. per cent. Blood chlorides were diminished and the CO<sub>2</sub> combining power of the blood was elevated due to loss of chlorides through the colon or because of vomiting. Gastric retention was not marked although vomiting was frequent and was thought to be due to the irritating action of the colonic contents. No studies on blood vitamins were carried out. In one patient with preoperative tetany there was a marked diminution in blood calcium. In four patients methylene blue introduced into the rectum was promptly recovered through an indwelling gastric tube.

*X-ray examination.* In two cases x-ray revealed a communication between the colon and jejunum rather than between the stomach and colon. In one case no fistula could be seen on x-ray. In all the others the barium entered the stomach promptly when given by enema. In one case a jejunal penetration was diagnosed. In the others there was no mention of a separate jejunal ulcer. However, the jejunum bordering on the anastomosis was irritable and irregular.

*Pathology.* As already stated, the lesion is one that starts primarily as a marginal or jejunal ulcer and subsequently penetrates the colonic wall to produce a fistula. The adjacent mesentery of the anastomotic loop, the mesocolon of the root of the mesentery, singly or in combination, may be involved in an intense inflammatory process. These structures are thickened, friable and edematous. When this inflammatory reaction is especially intense a fresh, fibrinous exudate may be seen on the mesocolon or mesentery of the jejunal loop. The mesenteries may be shrunken as the result of much cicatrization. Not

infrequently this combined pathological involvement gives rise to a large inflammatory tumefaction consisting of colon and jejunum with their accompanying mesenteries. In some of our cases the mass was found to be fist-sized; numerous adhesions of the omentum to the abdominal wall and of the stomach to the under surface of the liver were present. The original duodenal ulcer cicatrizes and heals unless the gastroenterostomy has ceased to function. Ginzburg and Mage (4) drew attention to the fact that only in a few instances does a gastroenterostomy fail to bring about healing of a duodenal ulcer.

#### TREATMENT

*Prophylaxis.* Before discussing therapy in gastrojejunocolic fistula emphasis should be directed to its prevention. It has been aptly stated that recurrent ulcer in or about the stoma is "man made." We believe that the operation of choice for duodenal ulcer is gastrectomy with resection well above the reentrant angle of the stomach and beyond the pylorus in an effort to produce an anacidity. We believe that an anterior anastomosis will circumvent the possibility of a colonic fistula should an anastomotic ulcer supervene in a small percentage of patients who still secrete acid. A recurrent ulcer without intimate relationship to the mesocolon is technically much easier to deal with. Occasionally gastroenterostomy becomes necessary in the old, poor-risk patient. The opening in the transverse mesocolon should be made as far away from the colon as the anatomical pattern of this structure will permit.

*Pre-operative preparation.* In no other group of patients is intensive pre-operative preparation more necessary and important for a successful outcome. The metabolic disturbances attendant upon obstruction, dehydration, avitaminosis and anemia have been recounted. The loss of gastric secretion through the fistula results in various degrees of alkalosis and hypochloremia. Guides to adequate preparation are furnished by repeated observations of the blood urea, blood chlorides, serum-proteins and the carbon-dioxide combining power of the blood. The estimated loss of approximately six liters of fluids excreted normally in the upper intestinal tract and reabsorbed in the ileum and colon, but which in the presence of a gastrocolonic fistula is "side-tracked" emphasizes the pre-operative preparation problem. Anemia should be rectified by repeated transfusions until the hemoglobin level has been raised to within normal limits. We have found that hemoglobin values should be verified constantly inasmuch as the effects of transfusions are transitory until well in the postoperative period. Inasmuch as absorption from the gastrointestinal tract is interfered with, vitamins must be administered hypodermically in an effort to correct the deficiency. Thiamine chloride (0.65 Gm.) and 100 mg. of nicotinic acid are administered daily along with large doses of ascorbic acid. Plasma proteins are supplied in the form of parenterally administered hydrolysed casein (amigens). The importance of a low plasma protein level particularly as this disturbance effects tissue edema and gastric emptying time has been stressed by Ravdin (5) and his coworkers. Plasma infusions are used in addition to the amino-acids to raise the depleted blood proteins. To supply the depleted blood chlorides 1500 cc.

of physiological salt solution is administered daily along with a similar amount of 5 per cent glucose in distilled water. The amount of sodium chloride excreted daily in the urine is a good index of chloride balance. It has been substantiated that a urinary excretion of 3 Gm. of sodium chloride is consistent with a positive chloride balance. Collier (6) has recommended that for each 100 mg. per cent the plasma chlorides need to be raised in order to reach the normal 560 mg. per 100 cc., the patient should be given 0.5 Gm. of sodium chloride per Kg. of body weight. Every effort should be made to rid the stomach of its foul, retained secretions. This is best accomplished by repeated gastric lavages followed by the use of the indwelling gastric tube through which nourishment and antacid medication may be introduced by the continuous drip method. Since the advent of the non-absorbable sulpha drugs (sulfasuxadine and thalidin) we have been administering them in an effort to reduce the bacterial content of the colon. Every effort should be made to diminish the frequent, watery bowel movements. Bismuth compounds and opium have been used for this purpose. When the blood calcium level is low calcium gluconate, intravenously, should be employed. We have found that the average time required for adequate preparation for operation is about a week. This naturally varies with the degree of physiological derangement.

#### OPERATION

*Anesthesia.* Much importance is placed upon a smooth well conducted anesthesia. A continuous spinal anesthesia as described by Lemmon (7) has been used in most of our cases. Relaxation and smoothness of respiratory movement is of paramount necessity. The anesthesia is by nature of the operation a lengthy one and the introduction of the anesthetic agent as required in various phases of the operation, as for duodenal closure and high gastric section, where relaxation is particularly required, facilitates and expedites the operative procedure. More recently we have used intratracheal anesthesia with curare. Either method expertly administered will prove satisfactory. Supportive therapy throughout the course of the operation in the form of a continuous intravenous drip supplemented by blood transfusions as blood pressure determinations indicate is essential to counteract shock and loss of blood.

*Operative treatment.* The indication for operative treatment in gastrojejuno-colic fistula is absolute. The prime consideration is to abolish the fistulous connection with the colon. Theoretically operation should entail disconnection and restoration of the structures involved in the fistulous communication (stomach, colon and jejunum). While gastric resection is ordinarily desirable at the time of the operation for the repair of fistula it is not always feasible or safe. The marked inflammatory induration and inflammatory exudate surrounding the colon and jejunum does not always permit safe separation and suture of these structures. Post-operative peritonitis due to peritoneal contamination at the time of operation but more frequently due to the insecurity of sutures placed in indurated tissues with subsequent leakage was the main factor in a high operative mortality. Before the recognition of these factors Pfeiffer (8) quotes

operative mortalities ranging between 25 and 63 per cent. Procedures to reduce this mortality were proposed by Schrimger (9) who advocated leaving the jejunal ulceration even though the colon were involved, resecting the stomach except for a cuff around the old stoma from which the mucous membrane was removed and the muscularis and peritoneal coats approximated. Allen (10) suggested an aseptic method of restoring normal stomach and intestinal continuity. Division of the stomach above the inflammatory tumor with performance of an anterior gastroenterostomy using a loop of jejunum distal to the previous anastomosis was suggested as a means of "short-circuiting" the fistula. Preliminary jejunostomy as a means of restoring fluid balance and placing the lesion at rest has been favored by some. We have not adopted this procedure in cases of gastrojejunocolic fistula although Colp and Druckerman (11) have emphasized its value and have employed it as part of the operative procedure. In the main, operative procedures as at present employed are limited to: (1) Resection of the fistulous tract with restoration of normal gastrointestinal continuity. This procedure is advocated where the inflammatory process is extensive and it is deemed unwise to prolong the operation by adding a gastric resection. It can only be employed if the pylorus is patent. It has been done in two cases in this series. One patient was exceedingly obese and it was felt unwise to subject the patient to the added risk of resection. It was realized that the duodenal ulcer would become reactivated. This was actually the case and the patient returned one year later with pyloric obstruction. A successful resection was then carried out. The other patient was a 69 year old man in exceedingly poor condition. (2) Resection of stomach and fistulous tract. Whenever feasible, this was the procedure of choice and was carried out successfully in five patients. (3) Stage operations. Pfeiffer and Kent (8) first advocated a diversionary colostomy in the ascending colon. We have employed this method in three cases—two in combination with the second procedure with gratifying results. In both cases there was marked improvement following the colostomy. In one patient belching of foul gas stopped, there was a significant gain in weight, and at operation for the cure of the fistula three months later the fistula was found spontaneously closed. Lahey and Marshall (12) also recommend that the operation be done in stages. The first procedure is division of the terminal ileum with performance of an ileo-sigmoidostomy. At the second operation the entire colon is resected beyond the fistula along with the stomach. The jejunum is dealt with as indicated. We have not used this procedure in any of our cases. We have not felt that preliminary cecostomy would be sufficiently diversionary if a staged procedure were planned nor have we added it in those cases done as a single operative procedure.

*Operative technic.* The abdomen is opened through a midline incision extending from the ensiform to the umbilicus. Where the x-ray shows a fistula far to the left (near the splenic flexure of the colon) a transverse incision in the left upper abdomen is recommended. Adhesions of the omentum to the anterior abdominal wall are divided and the stomach is separated from the under surface of the liver. The stomach and colon are lifted out of the abdomen and the ex-



tent and intensity of the inflammatory and indurated mass appraised. It is best to have a preconceived plan of procedure and the one that has served us best is proceeded with as follows. The finger bluntly penetrates the gastrohepatic ligament along the lesser curvature of the stomach thereby affecting an entry into the lesser peritoneal cavity behind the stomach above the site of the previous gastroenterostomy. This procedure will delineate a free area between the colon and the greater curvature of the stomach (gastro-colic ligament). This ligament is bluntly separated and ligated. It would perhaps be easier to divide the stomach proximal to the lesion at this stage and turning it to the right develop the structures entering the anastomosis with the posterior aspect completely in view. This would entail the addition of gastrectomy before it is completely established whether such an extensive procedure should be done at one time. After the gastrocolic ligament is divided the upper leaf of the mesocolon is separated from the stomach with great care exercised for the preservation of the middle colic artery. Dissecting above and below the colon, a finger can usually effect an entry into the mesocolon surrounding the site of anastomosis which is separated as completely as possible before the site of fistulous communication is entered. Once the colon is entered the opening is dealt with immediately to avoid contamination of the operative field. A clamp is placed above the stoma before the jejunum is cut away to prevent spillage of gastric contents and the jejunal loops identified and mobilized preparatory to reconstruction. If done in one stage a typical gastric resection is added. The duodenum will usually be found to be the seat of scar tissue as the result of a healed lesion. The opening in the mesocolon is closed and an anterior end to side gastrojejunostomy (Hofmeister) completes the procedure. A jejunal loop distal to the site of jejunal reconstruction is selected. This loop should be as short as the anatomical situation permits. A complementary jejunostomy of the Witzel or Kader type which is brought out through a small stab wound is added when it is feared that post-operative atony may ensue.

*Management of the jejunum.* Reconstruction of the jejunum may be simple or extremely complicated and difficult. Where the ulcer is truly marginal and not much of the jejunal wall is involved a simple closure of the jejunal opening in two layers can be readily effected. In the presence of a short afferent loop with a deep penetration or perforation into the root of the mesentery close to the fossa of Treitz, jejunal reconstruction offers a difficult problem. The lesion here is jejunal rather than marginal and the tissue induration and friability extreme. End to end suture is hazardous. It may be necessary to mobilize the third portion of duodenum and effect a closure of jejunum after transferring it behind the mesentery of the small bowel. After closing the distal jejunum a relatively safe side to side duodeno-jejunostomy is then performed. Where the afferent loop is of sufficient length an end to end or end to side anastomosis is done. In performing an end to end or plastic reconstruction of the jejunum it is essential that there be no encroachment upon the lumen particularly when gastrectomy is performed as we have seen leakage from the duodenal stump as the result of back pressure when the jejunum was narrowed. In this series jejunal



resection with end to end anastomosis was done four times, end to side jejuno-jejunosomy once and plastic reconstruction twice.

*Management of colon.* The opening in the colon is usually surrounded by inflammatory tissue which is excised to permit introduction of sutures in relatively normal tissue. As a rule the opening can be simply closed in a transverse direction using interrupted sutures without compromise of the bowel lumen. In one case the lesion was so large as to require a resection of the involved bowel. In this case no immediate anastomosis was carried out. The two limbs of colon were exteriorized.

*Post-operative therapy.* The indwelling gastric tube is connected to a suction apparatus and is removed at the end of 48 hours. After this, the tube is passed at night to insure against gastric retention. When jejunostomy is done a continuous drip of a specially prepared aliment is introduced by the drip method. Fluid balance is assured by a continuous intravenous drip and plasma and whole blood are supplied as required. Efforts are made to get the patient out of bed early to insure adequate diaphragmatic excursions. Excessive bronchial secretions are bronchoscopically aspirated and the patient is encouraged to expectorate. We have used penicillin pre- and post-operatively and feel it has reduced the incidence and severity of post-operative pulmonary complications.

#### SUMMARY

Our experiences with the management of gastrojejunocolic fistulae have been reviewed. Whereas ideally operation should aim to excise the fistula and reconstruct the parts along with gastrectomy each case must be evaluated individually. In some, the general condition of the patient will contraindicate so lengthy a procedure. In others the local condition because of its size and infectious potentiality will warrant a staged procedure. Eight cases are recapitulated. In some, operation was completed in one stage. In others, ascending colostomy was done as a preliminary procedure. There was one death.

#### CONCLUSIONS

Gastrojejunocolic fistula is a life threatening complication of gastroenterostomy. As opposed to gastrojejunal ulcer which may respond to medical management the operative indication in the former is absolute. The technical procedure is difficult and time consuming. The operative mortality which was formerly extremely high can be kept low by adequate pre-operative preparation and the selection of a staged procedure. Gastrectomy should be part of the operative procedure whenever feasible.

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## DELAYED PENICILLIN SENSITIZATION REACTION

### BRONCHIAL SPASM

JEROME L. KOHN, M.D.

(New York, N. Y.)

A delayed sensitization reaction to penicillin is not unusual. Cutaneous manifestations, such as generalized urticaria, toxic erythema, maculo-papular eruption and vesicular dermatitis are the most frequently seen. Adenopathy, joint swelling and edema as seen in serum sickness have occasionally been noted. Symptoms of severe bronchial spasm are very unusual. To our knowledge this latter symptom has not been recorded in young children. We wish to report on such a reaction.

### CASE REPORT

*History.* P. P., a white boy, aged 2 years, was irritable and had a temperature of 40° C. Soon after the appearance of these symptoms, he had a generalized convulsion of about fifteen minutes duration. Within a few hours the child began to vomit and had frequent watery bowel movements. The vomiting ceased after six hours. The patient was given sulfadiazine in the usual dosage for four days without any improvement in the diarrhea. He was then given three intramuscular injections of a peanut oil, bee's wax penicillin mixture of 300,000 units each. (This child had never received any penicillin previous to this illness. There was no history of allergic manifestations in the child or in the family.) The temperature reached normal levels within six days. The bowel movements became less frequent. Six days after he had received the last penicillin injection, the child was playing out of doors, and the mother noticed that he was having difficulty in breathing and was coughing spasmodically. Within four hours, after the onset of these symptoms, the child was admitted to Mount Sinai Hospital on July 5th.

*Examination.* The temperature was 38.5° C. The child was breathing with difficulty and was moderately cyanotic. There was dilatation of the alae nasi, retraction of the intercostal muscles and the diaphragm. The respiratory rate was 65 per minute. The posterior pharynx was not injected. There was moderate suppression of the breath sounds over both lungs. No sibilant rales were heard. The heart sounds were of good quality. Large indurated, moderately tender areas with bluish red discoloration were seen on both buttocks. The indurations were at the site of the previous penicillin injections and had not been present when the child had been seen three hours before admission.

*Laboratory data.* The blood count on admission showed a hemoglobin of 95 per cent, 22,000 white blood cells with 65 per cent polymorphonuclears, 29 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophiles. Six days later the hemoglobin was 70 per cent, 6,700 white blood cells, 38 per cent polymorphonuclears (of which 27 per cent were segmented), 60 per cent lymphocytes, and 2 per cent monocytes. No eosinophiles were noted. A roentgenogram of the chest showed no abnormalities.

*Course.* Soon after admission, the patient was given a subcutaneous injection of 0.2 cc. of adrenalin hydro-chloride-1:1000 dilution in aqueous solution. Within a few minutes there was definite relief of the bronchial spasm. It was necessary to repeat this injection of adrenalin only once. It was not necessary to use oxygen therapy.

Within two days the child was comfortable, there was no suppression of breathing. A few scattered sibilant rales were heard. The induration of buttocks gradually subsided.

On July 10th, five days after admission, an intradermal injection of 500 units of commercial penicillin in 0.02 cc. of physiologic saline was given. There was no immediate or

delayed reaction. Simultaneously at another site, 2,000 units in 0.1 cc. were injected in tridermally. There was no delayed reaction. A trichophyton test with 0.1 cc. of a 1:30 dilution of trichophyton (*T. Mentagrophytes*) was also negative.

Frequent soft bowel movements containing mucus, streaked with blood, persisted for about seven days. A bacteriological examination of the feces revealed no pathological organisms. Blood agglutination determinations showed a positive reaction to *Salmonella* A in dilution of 1:640 and to *Salmonella* B in a dilution of 1:5,120.

He was discharged two weeks after admission, apparently well.

# DISCUSSION

It is important to realize that following the injection of commercial penicillin there can be severe delayed reactions similar to those seen in serum sickness. In our patient the outstanding symptom was a severe bronchial spasm. The only other symptom was, large indurated areas on both buttocks, at the site of the original injections. This latter reaction first appeared several hours after the onset of the bronchial spasm.

There is usually a multiplicity of symptoms in serum sickness. In contrast to this picture our patient had only the two symptoms described above. This type of reaction is sometimes called local serum sickness. Ratner (1) says that the size of the inoculum determines the extent of the symptoms. The appearance of a reaction at any given place must depend on sufficient antigen to produce cell changes.

Local serum sickness must not be confused with local serum anaphylaxis which occurs only in individuals who have previously received a foreign protein. For example, Lucas and Gay (2) reported such anaphylactic reactions in children who had had prophylactic injections of diphtheria anti-toxin every three weeks while in a hospital ward. The incidence of the local reactions increased with successive doses and was characterized by redness and induration, and only rarely was there a small area of necrosis. It is important to remember that our patient had never had any penicillin before this illness.

Schwartzman (3), Rich (4) and others believe that an anaphylactic reaction can be significantly influenced by an intercurrent infection. In our patient the symptoms of the *Salmonella* infection were still present at the time of the anaphylactic reaction and it is possible that this infection may have been related to the severity of the symptoms.

Price, McNairy and White (5) reported on an adult who had symptoms somewhat analogous to those in our patient. The symptoms in their patient were more general and more severe. He had been given intramuscular injections of commercial penicillin for eight days. Four days after the last injection he had a very severe bronchial spasm, urticaria and high fever, became very cyanotic and was comatose. He was placed in an oxygen tent. Frequent subcutaneous injections of adrenalin gave temporary relief. It was seven days before all evidence of bronchial spasm had disappeared. An intradermal test to penicillin was negative.

There is a tendency to ascribe the delayed reaction to impurities in the preparation of the penicillin. In our patient, in addition to the usual impurities,

there were peanut oil and bee's wax. Crieep (6), using the serum of patients who gave a delayed reaction, in passive transfer tests, occasionally obtained a positive skin reaction with 1:1,000 dilution of the impure drug. He could not demonstrate any anaphylactic antibodies to penicillin. He believed that there was evidence of some immune substances in the serum of patients, but their exact role was unknown. He felt that the sensitivity was due to penicillin and that the substance had allergic potency. Therefore the reaction should not be attributed to toxic impurities or the medium used.

Penicillin is a chemical substance. It is possible that in some substances the drug is coupled with a protein which may assume changed antigenic properties. Landsteiner proposed that the term "hapten" be used for such serologically active combinations. Up to the present, there is no authentic evidence of "hapten" formations with penicillin. McClosky and Smith (7) sensitized guinea pigs by subcutaneous and intraperitoneal injections of commercial penicillin. The animals after an incubation period were injected with the antigen. Other tests were made on the isolated uterus, using the Schultz-Dale technic. Sensitization reactions were atypical and not uniform. They lacked permanence as contrasted with the reaction of animals who had been sensitized with true proteins. The authors were of the opinion, however, that the antibody-antigen combination obtained was due to the penicillin.

However, our present knowledge concerning pure penicillin is incomplete. Therefore it is impossible to determine whether the penicillin itself or some substance in the commercial preparation was the sensitizing agent which produced the anaphylactic reaction in the patient discussed in this paper.

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## A STUDY OF SEVENTY SUCCESSFULLY TREATED CASES OF STERILITY

J. KOTZ, M.D., F.A.C.S. AND MORTON S. KAUFMAN, M.D.

(Washington, D. C.)

*From the George Washington University Medical School*

When, in 1920, the senior author first began the practice of medicine, sterility was a hopeless problem. Diagnostic procedures were unknown, and the only therapy consisted of repeated dilatations and curettages. As many as ten curettages were sometimes done on a single patient.

If the patient consulted a surgeon after having had several curettements, a laparotomy was advised. The tubes were exposed and a fine wire probe was inserted into the fimbriated end of the tube in an effort to find and overcome the obstruction. If no obstruction existed before the operation, there was a strong possibility that it would after operation. One of our distinguished gynecologists even devised a special curette, the purpose of which was to remove any obstruction at the uterotubal orifice. Investigation of the semen was seldom done.

Such was the plan of treatment carried out until Dr. Rubin's article appeared in the Journal of the American Medical Association, April 10, 1920, describing tubal insufflation, and giving us a simple and accurate method for determining tubal patency. Dr. Rubin's article made no claims for the test other than that it was a diagnostic procedure that would, in a few minutes, give reliable information as to tubal patency. We, who are interested in the study of sterility, know that it is not only a diagnostic procedure, but a valuable addition to our therapeutic armamentarium.

Dr. Rubin's article gave us the first ray of hope in the treatment of the sterile patient. It stimulated research in a subject which had been sadly neglected, until, at the present time, we have a number of diagnostic aids in our search for the cause for sterility.

Through the use of this test much needless surgery, that would have resulted in some mortality, has been avoided. Many homes have been enriched by the presence of children where otherwise there would have been none.

It has been our purpose in this presentation to determine what factors have been chiefly responsible for sterility in those patients who subsequently became pregnant. We have chosen the last seventy successful cases from our files for this study. Fifty-six of these were cases of primary sterility and fourteen were secondary. The average duration of the sterility was 37.8 months, the longest being 168 months and the shortest 6 months. No patient was treated for sterility of less than one year's duration unless some special circumstance obtained (fibroids, age of 35 or over, etc.). The average age of the patients was 28.2 years, the youngest being 18 and the oldest 39.

The average duration of treatment, from the date of the first office visit to the date of the last period, was 8.48 months. The longest period of treatment

was 48 months, but in most cases in which treatment lasted over one year, treatment was intermittent rather than continuous. There were seventeen cases in which treatment lasted only one month.

Of these seventy patients, five had no discoverable cause for their sterility. One of these conceived in the month following the study after a sterility of one year's duration. One conceived three months after the study after a secondary sterility of three years' duration. Three were put on schedules of sex relations, two conceiving in one month following a sterility of one year, and the other conceiving in two months after a sterility of 14 years.

Twenty-seven patients exhibited only one cause for sterility. In three of these, the husbands showed an azoospermia, and pregnancy was accomplished by the use of artificial insemination with a suitable donor. One of these patients has had two successful artificial inseminations. One case had complete occlusion of the tubes, both to gas and lipiodol. A successful plastic operation on the tubes was performed in this case.

In the remaining twenty-three cases, seven showed only hypothyroidism, five showed some degree of tubal occlusion, four husbands exhibited low sperm counts, three patients had pelvic inflammatory disease, two had infantile uteri and two had infected and eroded cervixes. Complete studies were done on all of these patients except the three with pelvic inflammations. No inflations or endometrial biopsies were done on these patients.

There were thirty-two patients in whom there were two discernable defects. Twenty of these patients had some interference with the passage of gas through the tubes. Twenty of the husbands showed some diminution of cell count. Twelve cases had a lowered basal metabolism and/or marked obesity. There were five cases of abnormalities of the endometrium, three patients with infantile uteri, two with rather marked degrees of anemia, one with a retroverted adherent uterus, and one with a cervical polyp.

There were six cases with three discernable defects. All six showed some diminution of sperm count. Four had hypothyroidism, three had partial tubal occlusion, two had infantile uteri, and three had abnormal endometria.

In all groups, there were three cases which showed azoospermia, five cases in which no defect was found, thirty cases with some degree of oligospermia, twenty-eight cases with some degree of tubal occlusion, one case of complete tubal occlusion, twenty-three cases of hypothyroidism and/or obesity, eight cases that exhibited abnormal endometrium, five infantile uteri, and a number of miscellaneous conditions.

All of the patients with hypothyroidism and/or obesity received thyroid in appropriate doses and diet where indicated. All of the patients with partial tubal occlusion received repeated insufflations. Pelvic pathology was corrected by appropriate measures such as surgery, diathermy, cauterization, etc. Twenty-three husbands were referred to a urologist for therapy and the other seven were instructed as to diet, rest, and frequency of sex relations.

These seventy patients have had 85 pregnancies since their sterility studies were started. There have been 77 infants delivered, including one set of twins.

Seven patients have aborted, one having missed abortion. There have been two tubal pregnancies. Of the live births, one child had a spina bifida, hydrocephalus, and club foot and expired soon after birth, one was born at 8 months, weighing 4 pounds and survived.

#### COMMENT

There were seventeen cases in which pregnancy occurred within two months of their initial office visit, although they had been sterile for periods varying from seven months to fourteen years. In each of these, the diagnostic study was completed but therapy had not yet been instituted. Tubal insufflation is the only diagnostic procedure which has any therapeutic value, and we must therefore conclude that, omitting the possibility of a chance pregnancy, all seventeen became pregnant as the result of a single inflation.

Varying degrees of sperm deficiency was a finding in thirty cases. We must therefore conclude that oligospermia responds well to treatment, or that mild deficiencies of sperm count are not as important as we have been led to believe.

A low sperm count may improve under treatment, and occasionally a patient may become pregnant in spite of a low count. The following case illustrates such an occurrence.

Mrs. H. G., age 28, white. Secondary sterility. One previous pregnancy five years before by former husband. Trying for pregnancy one year. Husband in good health, age 42. Patient's physical examination and sterility study essentially negative. Report from urologist on November 2, 1943.

"Seminal specimen consisted of  $2\frac{1}{2}$  cc. of fluid. Normal in coalescence and viscosity. There is a 25 per cent reduction in numbers, and 25 per cent of the cells present have no motility. The morphology of the cells is normal. Motility of those cells possessing it is normal in character and longevity. Fertility is estimated at 50 per cent."

Patient's last period was January 4, 1944, just two months after the urologist's report. The patient gave birth to twin girls on October 5, 1944.

From our data, we may conclude that patients with endocrine dysfunctions except those of the thyroid accompanying their sterility respond poorly to treatment. Of the many patients with abnormal endometria, only 8 were treated successfully, in spite of a variety of endocrine treatments.

Patients with partial tubal occlusion, on the other hand, especially if that is the only defect, have an excellent chance of achieving success. Repeated inflations will frequently open the partially occluded tubes so that a successful outcome may ensue.

We regret that time did not allow us to report, from our files, on all the sterility cases who have become pregnant since 1921. However, we feel that this study of 70 patients reveals some pertinent facts.

From our figures, we must conclude that partially occluded tubes, oligospermia, and hypothyroidism are the three causes most amenable to treatment. Minor surgical conditions may also be successfully treated. Surgical treatment of completely occluded tubes is only rarely successful. It is not to be recommended unless the patient is fully advised of the remote possibilities for a suc-

cessful result. Endocrine deficiencies, with the exception of hypothyroidism, offer a less optimistic prognosis.

Of the therapeutic measures available, tubal insufflation still ranks as the most successful.

As a diagnostic procedure, tubal insufflation gives us information not only as to the patency of the tubes, but also as to the location of any obstruction that may be present, as well as to the presence of peritubal adhesions.

The world owes to Dr. Rubin an everlasting debt of gratitude. The application of his test has been directly responsible for untold happiness in many thousands of homes. His contribution to this subject has been the inspiration for all of the subsequent research which has brought the study of sterility to its present plane, and will carry it to new achievements in the future. The man himself has the acclaim and appreciation of our profession for his brilliant judgment, his keen mind, and his endearing personality. His writings, lectures, and personal encouragement have been largely responsible for our increased interest in and knowledge of the problem of sterility.

## IMPERFORATE HYMEN RESULTING IN HYDROMETROCOLPOS AND HEMATOCOLPOS

JEROME S. LEOPOLD, M.D.

*Formerly Director of Pediatrics, Lenox Hill Hospital; Clinical Professor of Pediatrics,  
New York University College of Medicine, New York, N. Y.*

Imperforate hymen resulting in hydrometrocolpos in infancy and in hematocolpos at puberty is a condition which is very infrequently encountered by pediatricians. Hydrometrocolpos is usually observed during the first two months of life. According to Kereszturi (1) who made an extensive search of the literature in 1940, only seven cases of this condition have been reported. Five of the patients were under two months of age. One was six years of age, and the other seven years of age. Kereszturi's patient was eight weeks of age when she first came under observation. In the same year Mahoney and Chamberlain (2) reported three additional cases all under three weeks of age.

### HYDROMETROCOLPOS

In this condition, there is present a marked distention of part of the genital tract. This is caused by complete obstruction of the vagina due to an imperforate hymen. Obstruction alone does not cause symptoms until puberty, when there is an accumulation of menstrual blood above the point of obstruction and hematocolpos results. According to Ladd and Gross (3) an additional factor must be present for the development of hydrometrocolpos in the period shortly after birth. The explanation presumably lies in the fact that a sufficient amount of estrogenic substance is absorbed from the maternal circulation to stimulate the infant's cervical and endocervical glands into abnormal secretory activity before birth and for a few weeks thereafter. Hydrometrocolpos depends upon a mechanical obstruction of the vagina and an unusual secretion by the glands of the uterine cervix.

Hydrometrocolpos, if of sufficient size, appears as a lower abdominal swelling. Due to pressure there may be urinary, intestinal or respiratory symptoms. The cause of the symptoms is immediately apparent if one examines the vagina and the rectum. A bulging imperforate hymen is apparent with bluish membranes. Rectally a fluctuant mass is palpable anteriorly in the vagina.

Treatment consists in a simple large incision or excision of the imperforate hymen under strict surgical asepsis. If the condition is not recognized an extensive surgical procedure may be performed with possible unfortunate results.

### ILLUSTRATIVE CASE<sup>1</sup>

The patient was a twelve-day-old infant who was apparently in perfect health at birth and weighed seven pounds and twelve ounces. A few hours before the examination there was noticed a slight distention of the abdomen. The stools were greenish-yellow and

<sup>1</sup> This patient and the other to be reported here were operated on by Dr. De Witt Stetten, to whom I am indebted for the operative notes.



contained curds. The abdomen gradually became more distended, with a bluish discoloration of the entire abdomen and of the lower extremities. The umbilicus protruded. The patient had apparently been voiding normally. There was little result from a rectal irrigation. Some bloody mucus was expelled from the rectum. The infant had regurgitated some of its feedings.

Examination revealed a well-nourished infant. There was marked distention of the abdomen with protrusion of the umbilicus. The entire abdomen and the lower extremities were cyanotic. The cyanosis was due to pressure on the pelvic vessels. The abdomen was tense, and in the lower half there appeared to be a firm resistance. A definite cystic mass was felt in the pelvis. There was blood on the examining finger on rectal examination. The temperature was normal. The remainder of the examination was negative.

A tentative diagnosis of intestinal obstruction was made, possibly due to intussusception.

Operation was performed immediately. A median epigastric hypogastric laparotomy was done. On opening the abdomen there was found a large thin-walled cystic mass which filled the lower abdomen and extended into the pelvis. Behind this cystic mass was another somewhat smaller cystic mass which seemed to fill the pelvis and was adherent to the other cystic mass. On further exploration it was found that dilated uretersex tended to the base of the anterior cystic mass and that these ureters could be followed up to dilated kidney pelves. On the superior surface of the posterior cystic mass were found a normal uterus, tubes, and ovaries. The anterior mass was obviously the distended bladder. A catheter was passed through the urethra and there was evacuated about 150 c.c. of clear urine with complete collapse of the anterior cystic mass. The bulging hymen was incised. About 100 c.c. of a thick milky fluid was evacuated. Immediately there was a collapse of the posterior cystic mass. Culture of the vaginal fluid revealed no growth. The operation was well-borne by the infant. For the following four days the infant's condition steadily improved. On the fifth postoperative day, however, the stools became very numerous and watery and there was a rise of temperature to 102.4°F. The infant became steadily worse and expired on the ninth day after the operation. Autopsy findings revealed the presence of bilateral hydroureters and bilateral hydronephroses.

#### HEMATOCOLPOS

Imperforate hymen causing hematocolpos is not a particularly rare condition. It is not observed very frequently and is often unknown by pediatricians because it occurs after the onset of puberty, usually between the ages of eleven and thirteen, when the patient is no longer under the observation of the pediatrician.

The condition is usually discovered when the uterine discharge of blood accumulates behind the imperforate hymen. The accumulation of blood increases in size with each menstrual period and eventually causes pressure symptoms. The patient complains of low abdominal pain, amenorrhea, urinary difficulties, and occasionally, of a distended abdomen, and abdominal mass. The cause of the symptoms is immediately apparent upon a vaginal and rectal examination when a bulging imperforate hymen is found with bluish membrane. Rectally the cystic mass is palpable anterior to the vagina. The mass may ascend to the uterus and tubes. Once a diagnosis has been made, treatment is simple and consists of an incision of the hymen.

#### ILLUSTRATIVE CASE

The patient, aged twelve years, had complained of diffuse abdominal pain for the past week. The pain had localized in the right lower quadrant during the past few hours. There had been slight nausea, but no vomiting and no rise in temperature. The bowels

were regular, but on defecation there was some rectal pain. There was no difficulty in urination. The patient had not yet menstruated.

Examination revealed a thin, rather nervous child who did not appear acutely ill. There was slight tenderness, but no rigidity, in the lower abdomen, most marked in the right lower quadrant. No mass was felt. Rectal examination revealed that the pelvis was filled with a large cystic mass which compressed the rectum. It was about the size of a small orange. On examination of the vagina, there was found a moderately dense completely imperforate hymen which bulged slightly. Treatment consisted in aspirating the imperforate hymen under anaesthesia and removing about 5 c.c. of very thick molasses-like dark red bloody material. The hymen was then incised, and a very large amount of similar material was evacuated. Following this procedure the patient made an uneventful recovery.

#### COMMENT

Imperforate hymen resulting in hydrometrocolpos in infancy and in hemato-colpos at puberty, is frequently overlooked due to the fact that a rectal examination, and a vaginal inspection are not made. The diagnosis of imperforate hymen should be considered when there are bladder symptoms present with a history of no previous menstruation.

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## THE DEVELOPMENT OF THE SURGICAL TREATMENT OF GASTRIC AND DUODENAL ULCER DURING THE LAST FORTY YEARS

RICHARD LEWISOHN, M.D.

*(New York, N. Y.)*

Anniversary volumes afford a pertinent opportunity for reviewing the changes and developments which have occurred in medicine and its affiliated specialties during the active years of those who are to be honored on such occasions. Undoubtedly many contributors to this volume, better qualified for this work than this author, will stress the changes and improvements which have taken place during Dr. Rubin's forty active years in obstetrics and gynecology and his monumental contributions to these specialties.

For my part I have selected as my subject my personal experiences in a field in which I have been actively engaged for the past forty years, namely, the development of the surgical treatment of gastric and duodenal ulcer.

Modern gastric surgery dates back slightly more than sixty years for it was in 1881 that Billroth reported the first successful gastric resection for carcinoma. At about the same time, Woelfler (a Billroth pupil) performed the first gastroenterostomy for pyloric obstruction, using the antecolic long loop method. A few years later von Hacker introduced the retrocolic short loop anastomosis which shortly became the method of choice. Both methods are used by gastric surgeons today in connection with gastric resections. I have always preferred the retrocolic method which avoids stasis in the afferent loop.

It is interesting to note how often the antecolic Woelfler technic, now about sixty years old, has been rediscovered by various groups of surgeons. Even in recent years some surgeons, evidently not familiar with the literature, have advocated and used the antecolic method under the impression that they were introducing a new procedure.

The reader will undoubtedly be surprised to hear that during my three years' stay (1904-1906) as assistant at the Heidelberg Clinic I did not see a case of duodenal ulcer. The Clinic published an annual report of its surgical activities. The volumes of those three years are still in my library. The term: duodenal ulcer is not even mentioned. At that time duodenal ulcers were erroneously classified as pyloric ulcers. In benign lesions pyloric obstruction was the prime indication for operation and gastroenterostomy was the operation of choice. On the whole, gastric operations were rare. In 1904, 29 ulcer cases were operated at the Heidelberg Surgical Clinic; in 1905 the number dropped to 15. No partial or subtotal gastrectomies were performed for benign lesions. The small number of gastric operations for ulcer is even more surprising in view of the fact that the surgical service had over 200 beds. It may be of interest to point out that the Murphy button, now a practically obsolete instrument, was then used for every gastroenterostomy. I shall discuss later its definite advantages for re-establishment of continuity in resections for juxta cardiac ulcers.

The Clinic was directed by Professor Czerny, one of the ablest pupils of Billroth. He and Lembert independently described the first safe method for intestinal suture. Furthermore, he was the first to systematize vaginal hysterectomy (1879). He is shown here with his staff.

It may be of interest to point out that Voelcker, who was the "Oberarzt," performed the first successful resection of the cardia for carcinoma forty years ago.



FIG. 1. Professor Czerny and his staff, 1906

1. Professor Czerny, 2. Lichtenberg, 3. Nast-Kolb, 4. Voelcker, 5. Metzner, 6. Eloesser, 7. Werner, 8. Maas, 9. Hirschel, 10. Looser, 11. Arnsperger, 12. Lewisohn, 13. Baisch.

During the next 20 years surgeons began to attack lesser curvature gastric ulcer more radically, first by local excision with or without gastroenterostomy and later by sleeve resection. However, both excision and sleeve resections were followed by hour glass contracture of the stomach in so many instances that these methods were gradually abandoned, to be replaced by gastric resection.

I would like to digress here for a few minutes and discuss the proper terminology for operations for gastro-duodenal ulcers: specifically, I would like to warn against the abuse of the term "subtotal gastrectomy."

Subtotal gastrectomy means—as the word subtotal implies—the removal of practically the whole stomach. Only a small pouch of stomach is left *in situ*, just enough to permit establishment of an anastomosis with the jejunum. Such extensive resections are sometimes necessary in large gastric ulcers. They are never indicated—in fact they practically are never used in gastric resection for duodenal ulcer. Yet many surgeons use the term subtotal gastrectomy even when performing an antrumectomy, let alone a partial gastrectomy. I have

recently discussed in detail the importance of a correct nomenclature in gastric operations in a paper which I presented before the American Medical Association meeting in San Francisco. This paper will appear in detail in the Journal of the American Medical Association. For this reason I shall not discuss the subject here.

Figure 2 shows at a glance what is meant by partial gastrectomy, subtotal gastrectomy, or palliative resection. Unless these terms are used correctly the subject of gastric resection for gastro-duodenal ulcer will be hopelessly confused.

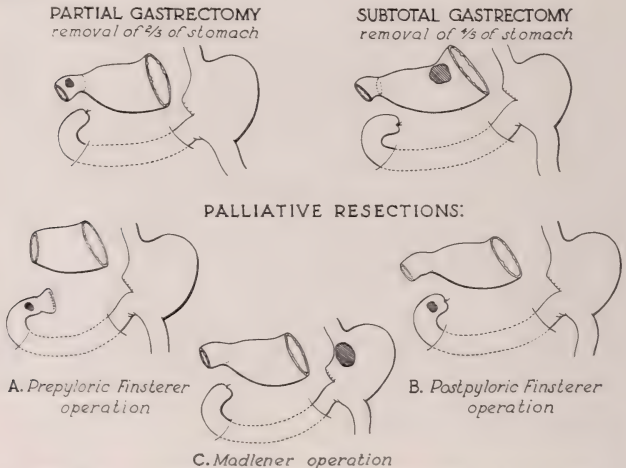


FIG. 2. Partial Gastrectomy; Subtotal Gastrectomy; Palliative Resections

### I. SURGICAL TREATMENT OF GASTRIC ULCER

We encounter practically complete unanimity as to the proper surgical treatment of gastric ulcers (with the exception of ulcers located close to the cardia). Partial or subtotal gastrectomy (dependent upon the size and location of the ulcer) is generally considered as the method of choice. The ulcer and the part of the stomach distal to the ulcer, including the pyloric ring, are removed and the continuity is usually re-established by the Billroth II technic.

Two methods are commonly used for this anastomosis: either the upper third of the remaining gastric pouch is closed and the lower two-thirds is anastomosed to the jejunum, or the whole circumference of the stomach opening is united by a two layer suture with the jejunum. The first method is usually called the Hofmeister technic, the second method the Polya technic. The reader may be surprised to hear that about 30 years before Hofmeister and Polya the



principles of both methods were described, the first by von Eiselsberg in 1889, the second by Kroenlein in 1887. Instead of Hofmeister and Polya methods, the procedures should rightfully be called Eiselsberg (1) and Kroenlein (2) technics (fig. 3).

All gastric ulcers, whether large or small, except the real juxta-cardiac type, should be subjected to partial or subtotal gastrectomy. The end results in this group of cases are excellent. I have never seen a gastrojejunal ulcer following a gastric resection for gastric ulcer.

The juxta-cardiac gastric ulcer (luckily a rare location for a gastric ulcer) deserves a special word. The removal of these ulcers would require a total gastrectomy. This procedure, while sometimes an operation of necessity in operations for carcinoma (with operative results improving steadily in recent years) is not warranted in gastric ulcers.

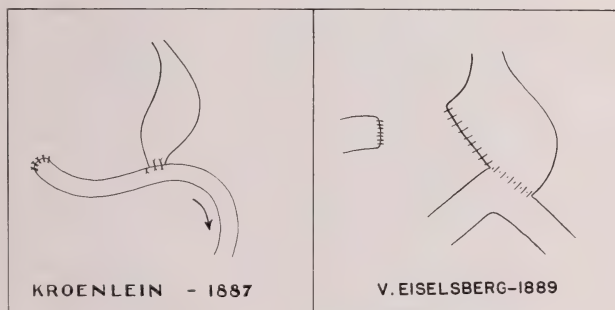


FIG. 3. Reproductions of the authors' original drawings

It is in the surgery of these high gastric ulcers that the use of the Murphy button deserves to be resurrected from the oblivion into which it has been relegated. Many gastric ulcers could safely be subjected to subtotal gastrectomy if the surgeon would use the button for the anastomosis. The Murphy button technic undoubtedly was of the greatest help in putting modern gastric surgery on the map. In fact, I have heard the late Dr. William Mayo state that "the Murphy button was the most ingenious surgical instrument ever invented". If just sufficient normal gastric wall is left on the lesser curvature to permit a safe closure of the cut end of the stomach, the Murphy button, if correctly used, will permit a safe re-establishment of gastro-jejunal continuity.

No surgeon can decide definitely by palpation whether a gastric ulcer is benign or shows early malignancy. For this reason the palliative resection (so called Kelling-Madlener operation) should be used only in very exceptional cases.

In order to effect a union of the small pouch of the stomach, which is not easily accessible under the arch of the ribs, with the jejunum a special technic for the

use of the button is necessary. This method was devised by my former chief, Dr. A. A. Berg, many years ago.

The Weir modification of the Murphy button is used. The Weir button has two broad flanges on the male half of the button, thus making it less apt to drop into the stomach. The female half of the button is dropped into the small remaining pouch of the stomach before its lumen is closed by layer suture. The jejunum is then picked up and an encircling stitch of Pagenstecher linen thread is applied, and a very small incision, which is subsequently stretched by an artery forceps, is made into the jejunum at about the center of the encircling



FIG. 4. Technic of Murphy button I

stitch and the button is inserted into the jejunum in the usual manner. The suture is then tied around the male end of the button which is thus anchored in the jejunum. A small opening is made in the colonic mesentery. The left hand of the surgeon takes hold of the gastric half of the button, which is usually found near the cardia, and draws it to the posterior wall of the stomach, some distance away from the gastric suture line. The button is placed against the gastric wall by holding it tightly between two fingers. A very small opening is made over the lumen of the button. With the aid of a surgical forceps the wall of the stomach is then pulled over the button so that the button protrudes from and is anchored safely in the gastric wall. By this technic, pursestring

formation of the gastric mucosa with the possibility of a leak is avoided. The two halves of the button are then united. Tight compression of the button is necessary for a safe closure. The opening in the colonic mesentery is attached either to the stomach or to the jejunum by a few interrupted stitches (figs. 4, 5, 6, 7).

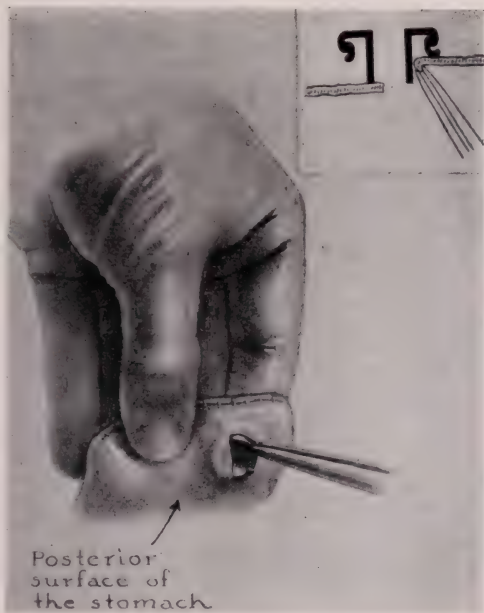


FIG. 5. Technic of Murphy button II

Undoubtedly some, though very few, gastric ulcers reach right up to the oesophagus. In these cases a safe suture of the gastric pouch is impossible. For such ulcers which cannot be removed surgically without undue risk to the patient Madlener in 1923 suggested leaving the ulcer in place and removing the distal half of the stomach. It is of interest to point out that although this operation goes by the name of Madlener (3), it was first described in 1918 by Kelling (4). Not only did Kelling suggest this operation, but he proved in eight cases that following this operation, the pre-operative free HCl of 30 or more was changed into a complete absence of free HCl. It is well known that the vast majority of gastric ulcers show some gastric acidity. The resulting anacidity following

the Kelling-Madlener operation sometimes effects complete healing and disappearance of the ulcer.

Kelling published his observations in 1931. They were recently repeated and confirmed by Colp and Druckerman (5) at Mount Sinai Hospital.

Perforation of a gastric ulcer into the free peritoneal cavity with secondary generalized peritonitis is comparatively rare, much rarer than an acute perforation of a duodenal ulcer. Hemorrhage from a gastric ulcer occurs occasionally and in some instances, namely in cases of continuous profuse hemorrhage, re-



FIG. 6. Technic of Murphy button III

quires immediate surgical attention in order to prevent a fatal issue. We shall discuss the treatment of perforation and hemorrhage in connection with their much more frequent occurrence in cases of duodenal ulcer.

## 2. SURGICAL TREATMENT OF DUODENAL ULCER

The surgical treatment of duodenal ulcer is even today a controversial subject. Great credit is due to William Mayo and Moynihan for describing duodenal ulcer as a clinical entity—and for reporting large series of cases treated by gastroenterostomy. Their early reports date back to 1910.

At first, simple gastroenterostomy was considered sufficient for the treatment of duodenal ulcer. Later, gastroenterostomy was combined with the exclusion

method either in the form of an infolding prepyloric stitch or a fascia strip. Eiselsberg divided the stomach in the prepyloric region. After these methods had been applied for a number of years, it was found that while the duodenal ulcer had healed as a consequence of the operation, some patients suffered from a more painful lesion, namely, a gastrojejunal ulcer. However, the figure quoted generally was not higher than 2 per cent and surgeons were not unduly alarmed.

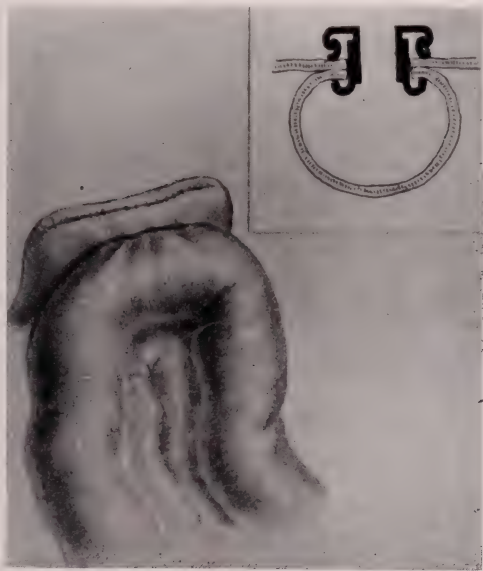


FIG. 7. Technic of Murphy button IV

In 1914 Mount Sinai Hospital introduced the grouping of surgical cases, the first hospital in New York to do so. Under this system all gastrointestinal cases were assigned to the service of Dr. A. A. Berg. We soon noticed that gastrojejunal ulcers were much more frequent than the 2 per cent figure usually quoted. We had a very careful follow-up system. Every Sunday morning Dr. Berg and his whole staff spent a few hours in the follow-up clinic. When I started to study our gastroenterostomies by personal interviews with the patients, the figure of gastrojejunal ulcers began to rise rapidly, until it reached the very high figure of 34 per cent in patients operated 5-10 years previously (6).

Naturally we were alarmed by these results. At about the same time Haberer



had made similar observations. However, he had gone one step further. In 1920 he began to supplant the popular method of gastroenterostomy (at least popular with the surgeons, if not with the patients) by a partial gastrectomy which removed the duodenal ulcer with one half to two thirds of the stomach.

In 1922 I made a special trip to Innsbruck in order to study Haberer's results. I feel that Haberer deserves a great deal of credit for advocating this new procedure of a direct attack upon the duodenal ulcer not only in easily removable ulcers on the anterior wall, but also on the posterior wall ulcers adherent to the pancreas. The gastric group under Dr. Berg, and later under my direction, have used partial gastrectomy as the method of choice in the surgical treatment of duodenal ulcer ever since 1922.

#### SECONDARY ULCERATION

When, in 1925, I reported the high incidence of gastrojejunal ulcers (34 per cent) following gastroenterostomies for duodenal ulcer, the argument was advanced that later studies from our service might show that partial gastrectomy would not reduce these high figures to any considerable degree. This question could not be answered until sufficient time had elapsed for a proper comparison of these two methods.

In 1935 we were able for the first time to compare the frequency of the gastrojejunal ulcers following gastroenterostomy and partial gastrectomy respectively. Mage presented before the Medical Fortnightly of the New York Academy of Medicine a five year follow-up of the results of partial gastrectomies performed by Dr. Berg and his associates between 1924 and 1929. A comparison of these results demonstrates a material reduction in postoperative gastrojejunal ulcers following partial gastrectomy as against gastroenterostomy. Instead of a 34 per cent incidence, we had one of 7 per cent (7) (Table I).

Approximately the same figures were reported by Mage in 1943 (8) when he reported an incidence of 7 per cent of gastrojejunal ulcers in 366 partial gastrectomies for primary duodenal ulcer performed by the gastric group of Mount Sinai Hospital between 1923 and 1940 (Table II).

In a panel discussion on ulcers before the New York Surgical Society last winter in which I had been invited to participate, I compared the figures collected by Mage (8) and myself. In the discussion which followed Mage stated that I was not justified in comparing these two statistical studies because whereas his figures had been evaluated mathematically by Hollander (9) my figures did not have the benefit of such mathematical evaluation.

Everybody knows that statistical studies can only be depended upon if the utmost accuracy is employed in evaluating the material. For a mathematical evaluation at least 90 per cent of the material should be available for review. With our shifting population in a large city like New York, this figure cannot be reached without a perfect follow-up system. Both Mage's and my statistics suffer from the same defect (50 per cent follow-up). For this reason a mathematical evaluation of data consisting only of 50 per cent of the actual cases seems without importance.

Mage tries to overcome this objection by assuming "that the incidence of failure among the group of unfollowed patients is no greater than among the observed group and it may be even less." I doubt whether many statisticians will agree with this statement.

In a statistical study of operated secondary ulcers only those cases should be included, in which the presence of an ulcer is proved by operation. Without such proof no case should be included in the statistical group. To clarify this point an illustrative case may perhaps be cited. In 1936 I had performed a subtotal gastrectomy on a patient for a jejunal ulcer. The pathological report of the resected specimen was: jejunal ulcer. Severe abdominal symptoms re-

TABLE I

*Comparison of follow-up results in gastro-enterostomy and partial gastrectomy for duodenal ulcers*

	CASES	OPERATION BETWEEN	REEXAMIN- ATION IN	GASTRO- JEJUNAL ULCER	PROVED BY OP'N
Gastroenterostomy.....	68	1915 and 1920	1924	23 cases (34%)	12 cases (18%)
Partial gastrectomy.....	82	1924 and 1929	1933	6 cases (7%)	1 case (1.2%)

TABLE II

*Mage's table of subtotal gastrectomies (1923-1940)*

TYPE OF CASE	OPERATIVE SURVIVORS	RECURR- ENCES	BASIS FOR DIAGNOSIS		
			Operation	Gastroscope x-ray	Gross Bleeding
I. Duodenal Ulcer.....					
(a) Primary*.....	366	27	6	16	5
(b) Secondary†.....	136	13	7	4	2
(c) Total.....	502	40	13	20	7
II. Gastric Ulcer.....	98	1	0	1	0

\* Primary case: no previous gastric operation.

† Secondary cases: one or more previous gastric operations.

curred soon after this operation. The clinical picture was complicated by the fact that the patient had a 4 + Wassermann. Gastroscoy revealed a distorted stoma. He was reoperated by another surgeon, with the diagnosis of a recurrent ulcer. Neither the specimen obtained at operation nor the post-mortem examination revealed such an ulcer. I feel that Mage was not justified in including this case among the 27 cases of recurring ulcers. A distorted stoma by itself does not prove an ulcer. It may have been due to the previous operation and the gastric symptoms may have well been caused by cerebrospinal lues. Nevertheless, this case was included by Mage among the cases which are the basis of the mathematical evaluation.

Mage has included 7 cases of recurrent painless hemorrhage with negative

x-ray findings in his series. Hemorrhage may be due to causes other than peptic ulcers (for instance, gastritis). Many people will feel that these cases should not have been included in a series of secondary ulceration.

These two examples—I could add a few more—show the importance of a correct interpretation of the individual cases which form the basis for subsequent statistical analysis. In their absence mathematical evaluations are of no significance.

A few words may be in order here about the method of conducting an effective gastric follow-up system. As stated above, a good follow-up system is most important for evaluation of results. Such an effective follow-up system requires not only the attendance of the whole group of surgeons and gastroenterologists interested in the special group, but a number of secretaries who keep the records and follow (possibly by home visits) those cases which do not keep their appointments.

If the chief of a surgical group fails to attend the follow-up clinic and turns the clinic over to a junior, patients will soon find out that the proper interest in the late results is lacking and will gradually fail to respond to their appointments.

Everybody should read and keep in mind the first two paragraphs of a paper published by the gastric group at the Presbyterian Hospital, New York, in 1939 (10):

"A follow-up clinic was organized in the Surgical Department of the Presbyterian Hospital in 1916. For the past 22 years, the senior members of the staff with their associates have spent one full morning each week in this clinic, studying and recording the results of surgical therapy. As a result of the clinic the intimate relationship between doctor and patient has deepened with time."

"An idea of the effort made by the surgeons and clinic aides and of the resulting response made by the patients in a large metropolitan community is gained from the following figures: namely, in the year 1935, 5983 patients were asked to return to the general surgical follow-up clinic; of these 5034 did return, 883 reported by letter, and only 66 or about 1 per cent were lost. It is only by such high incidence of interviews between doctor and patient months or years after operation, that accuracy in the estimation of results of therapy can be approximated."

An interesting group of cases has been reported, first by Haberer, later by others. In these cases a prepyloric Finsterer operation had been performed. A number of recurrent gastrojejunal and jejunal ulcers followed. These patients were cured only after removal of the pylorus. These observations demonstrated clearly the great importance which the pyloric ring plays in the formation of ulcers.

It has never been explained why duodenal ulcers are so frequent in men and so rare in women. Ninety per cent of the ulcers occur in the male and only 10 per cent in the female. The same proportion is observed in congenital pyloric stenosis. It is certainly most interesting that the preponderance of the male sex in the tendency to inflammatory diseases of the pyloric region is already evident in the new-born infant. To my knowledge this analogy between con-

genital pyloric stenosis of the baby and the gastroduodenal ulcers on the adult has not been mentioned in any discussion on the etiology of ulcers. It may give us a lead in applying hormonal therapy (so popular at present) to the treatment of ulcers.

Dragstedt (11) has advocated transthoracic and more recently subdiaphragmatic vagotomy for the treatment of gastroduodenal ulcers. It is too early yet to evaluate the results. At least five years must elapse before the results can be evaluated properly. The fact that free HCl is present after this operation would seem to indicate that this procedure may not solve the ulcer problem. I have always pointed out that surgical treatment of gastroduodenal ulcers is not the final answer. The solution will be found, when the gastroenterologists show us a way to make a hyperacid stomach anacid without destroying its mucous membrane.

Acute perforations of gastric or duodenal ulcers are not uncommon and require immediate attention. In this country simple suture of the perforation with drainage of the abdomen is the method of choice. On the continent of Europe many surgeons prefer to perform a partial gastrectomy when the patient reaches the hospital within 6-8 hours after the perforation and before a generalized peritonitis has set in. The reason for this more radical approach is the fact that a large percentage of duodenal ulcers are so-called "Kissing ulcers." The blow-out occurs in the ulcer on the anterior wall, but many patients continue to have symptoms, because the active ulcer on the posterior wall of the duodenum was naturally not affected by the simple suture of the ulcer on the anterior wall. Furthermore, large indurated perforated ulcers are occasionally seen which cannot be closed by simple suture. In this group of cases the major operation of partial gastrectomy seems the logical procedure.

Now a few words about bleeding duodenal ulcers. These hemorrhages may be mild or may be so serious that, unless treated surgically, the patient will die from an uncontrollable hemorrhage. Even when surgery is employed, some of the patients will succumb, especially when the operation is deferred too long. Statistics about bleeding ulcers have been confused hopelessly by many writers. We must separate these cases into three groups: Group I, the hemorrhage is mild and stops automatically without transfusions of blood; Group II, the hemorrhage stops after a few blood transfusions; Group III, uncontrollable hemorrhage.

If we—as many authors have done—group these 3 groups together in our statistics, we naturally paint a very favorable picture. If we separate Groups I and II from Group III, the picture changes completely. Without operation, Group III will have a very high mortality, not much lower than 90 per cent. Even with operation—especially if performed at a time when the tissues after continued hemorrhage have lost their healing power—the mortality will never be negligible. The cause of the hemorrhage in such cases is an ulcer on the posterior wall of the duodenum and the feeding vessel is usually the Art. pancreatoduodenalis. Partial gastrectomy with removal of the ulcer is the only logical procedure. Transfixion or cauterization of the ulcer or an attempt to ligate the

bleeding vessel will not be sufficient to stop the hemorrhage or to prevent its recurrence. It seems illogical to continue transfusions indefinitely. The following case is an illustration: A man, 41 years old, who had been operated 10 years previously for a perforated duodenal ulcer, was admitted to the hospital with profuse hemorrhage. He received 15 blood transfusions, during his stay in the hospital. He died on the sixth day. He should have been operated after three transfusions had failed to stop the hemorrhage.

It would carry us too far to discuss here the surgical treatment of gastrojejunal ulcers. They were—as I pointed out—most frequent in the days of gastroenterostomy. With partial gastrectomy their occurrence has been reduced materially.

Modern gastric surgery has travelled a long road during the last forty years. With proper selection of the cases and careful operative technic it affords a very fruitful and gratifying field for surgical endeavor.

Until a specific medical cure for ulcer is found or unless vagotomy should present satisfactory results after a five years' follow-up, gastric resection offers the only possible chance of a cure for gastro-duodenal ulcers which resist the well established forms of medical treatment.

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## EPITHELIOMA OF THE UTERINE CERVIX

JAMES C. MASSON, M.D.

*Division of Surgery, Mayo Clinic,*

AND

DAVID B. JUDD, M.D.

*Fellow in Surgery, Mayo Foundation,*

*(Rochester, Minnesota)*

In spite of more efficient methods of treating cancer and extensive educational programs to help the medical profession and the laity to recognize the early signs of this disease, we are confronted with the appalling fact that one death out of every seventeen is from cancer. Statistics also show that more women die as the result of cancer of the uterus today than previously. In 1936, 16,280 women (4) died in the United States from uterine cancer and of this number the uterine cervix was the seat of the primary lesion in about 11,000 cases.

At the present time the increase in the number of deaths from cancer of the uterus is real, not apparent. Some authors have suggested that this increase is the result of more accurate diagnosis. This seems unlikely, for the symptoms of advanced cancer of the uterus could hardly be confused with those of any other disease. One reason for the increase, of course, is preventive medicine and a higher standard of living, as the result of which more people live to the cancer age. Furthermore there is ample proof that dark-skinned women, such as Negroes in this country, who rarely had this disease sixty years ago now have it as frequently as white women.

The greatest difficulty in efficient treatment, and especially in the prophylactic treatment, of cancer is a lack of knowledge of its causation. It is known that heredity has a definite influence; at least a susceptibility or tendency to the disease is transmitted. It is also known that chronic irritation in susceptible people is often a predisposing factor. In the cervix, chronic infection or stricture probably plays an important part. While it is impossible to prove Cohnheim's hypothesis that all cancers start from embryonic, epithelial-cell rests, the hypothesis is nevertheless widely accepted, as it seems logical and cannot be disproved. All cancers, and in fact all malignant tumors, are made up of more or less normal cells in various states of development and they differ from those in other bodily tissue only in that they grow without apparent control and at the expense of normal tissues. Furthermore, cells from a primary growth, on being transported to other localities by lymph, by the blood stream or by ingrafting into an open wound, will continue to grow in a similar manner to that of the parent growth. Prolonged estrogenic stimulation has been suggested as a predisposing cause of cancer of the uterus.

If the presence of cancer is once accurately diagnosed by examination of a microscopic section, permanent cure can be obtained only by radical and efficient treatment. The type of treatment and the ultimate result of such treatment

will depend, not only on the extent of the disease, but also in large measure on the grade of malignancy present, as suggested by Broders (1) and Martzloff (2). Broders' classification, which takes into consideration the amount of differentiation of the cells in the active, growing portion of the tumor, is of great prognostic value. In a tumor of grade 1, there is little departure from the normal type of adult cell and, as a result, such tumors are of low degree of malignancy. Tumors of grades 2 and 3 show less differentiation and those of grade 4 show marked dedifferentiation and represent the most active type of malignant disease. Many pathologists do not place much value on the grading of malignant tissue and contend that sections from different parts of a single growth will suggest different degrees of malignancy. It has been said that tissue taken at different times may show various percentages of differentiation of the cells. There is no doubt that changes do take place and various factors like infection, degeneration and so forth influence the microscopic picture. After trial in a very large series of cases, however, we are satisfied that the method is of real prognostic value and we rely on it a great deal. There is no doubt that the training and personal equation of the pathologist are most important in evaluating the method.

The classification of Schmit (5), which takes into account the amount of local involvement, has been accepted by many gynecologists; it is a useful but by no means accurate method of tabulating cases. According to this classification apparently early lesions are grouped in stage 1; stages 2 and 3 include more advanced lesions and stage 4 represents the most advanced, hopeless lesions. We must not, however, be misled by fixation or infiltration in the broad ligaments, as this may be the result of a coexisting inflammatory disease or endometriosis, and malignant involvement of the vaginal vault can be removed satisfactorily along with the uterus. On the other hand, it is not at all uncommon at the time of operation on a small (stage 1) cervical lesion to find extension into the broad ligaments and obturator glandular involvement without any suggestion of uterine fixation on bimanual examination.

The extent of the local growth is no doubt of great importance from a prognostic standpoint and as an indication for treatment but it does not represent as good a guide to the ultimate outcome as the histologic appearance of the predominant cells. Experience has shown that the greater the differentiation or the more the cells of a tumor approach their normal histologic structure the greater the resistance to radiotherapy. For such tumors radical surgical removal gives the best results. Highly malignant tumors, however, with marked cellular dedifferentiation, respond more favorably in many cases to both roentgen rays and radium and, except in a very early stage, are difficult to cure by surgical measures alone.

It is hard to compare statistics of the present day with those tabulated from results obtained before the use of chemotherapy, scientifically given anesthetics and improved surgical technic with more importance placed on preoperative and postoperative care including transfusions, intravenously administered fluids and the diagnosis and treatment of atelectasis, pneumonia, peritonitis and venous

thrombosis. Furthermore, in the earlier statistics in the Mayo Clinic many operations performed for cancer of the cervix were listed as simply "total abdominal hysterectomy" and it is difficult to tell from the specimens whether a more radical operation was done than is indicated in benign conditions. Table I shows the five year results obtained according to grade of malignancy in 392 cases of epithelioma of the cervix in which operation was performed at the

TABLE I

*Effect of grade of malignancy (Broders' method) on prognosis following operation for epithelioma of cervix (1913-1940)*

GRADE	WERTHEIM HYSTERECTOMY			ALL PATIENTS OPERATED ON		
	Patients traced*	Lived 5 or more years after operation		Patients traced*	Lived 5 or more years after operation	
		Number	Per cent		Number	Per cent
1	0	0		3	3	100.0
2	13	12	92.3	50	32	64.0
3	44	29	65.9	179	106	59.2
4	20	10	50.0	99	37	37.4
Not stated	4	2	50.0	61	29	47.5
Total	81	53	65.4	392	207	52.8

\* Inquiry as of January 1, 1946, includes only those patients operated on five or more years prior to the time of inquiry; that is, 1940 or earlier. Hospital deaths are included in the calculations.

TABLE II

*Epithelioma of the cervix*

Hospital mortality rate by type of treatment 1910-1944

TYPE OF TREATMENT	PATIENTS	HOSPITAL DEATHS	
		Number	Per cent
Operation without irradiation.....	312	16	5.1
Operation with irradiation.....	438	4	0.9
Irradiation only.....	2,093	24	1.1
Total.....	2,843	44	1.5

Mayo Clinic from 1913 through 1940. In eighty-one cases the operation performed was listed as Wertheim hysterectomy whereas in 311 cases it was listed simply as total hysterectomy (abdominal or vaginal).

Table II shows the hospital mortality rate in a series of 2,843 cases in which the patients were treated at the clinic from 1910 to 1944, inclusive. Table III shows the five year survival rates by type of treatment for a series of 1,872 traced patients from 1910 to 1939, inclusive.

Cancer developing from the squamous cell epithelium of the cervix presents a different histologic picture and carries a graver prognosis than cancer developing

from the cylindrical gland-bearing cells that line the cervical canal. The former growths are known as "squamous cell carcinomas," "epitheliomas" or "epidermoid cancers" and they constitute about 90 per cent of all cervical cancers. Those developing from cylindrical cells are called "adenocarcinomas" and they constitute only about 10 per cent of cervical cancers.

If progress is to be made in the treatment of carcinoma of the uterine cervix it will be the result of specific treatment not known today and it will consist in prophylactic treatment against predisposing factors rather than active treatment of the condition once it has become well established. The early signs of cancer of the cervix are uniformly listed as irregular spotting, a foul, watery discharge and pain. Unfortunately these are generally the signs of a well-advanced growth but it is surprising how frequently one sees extensive involvement without bleeding, foul leukorrhea or pain.

TABLE III  
*Epithelioma of the cervix*  
Five year survival rates by type of treatment

TYPE OF TREATMENT	PATIENTS*		LIVED 5 OR MORE YEARS AFTER TREATMENT	
	Total	Traced	Patients	Per cent of traced patients
Operation without irradiation.....	259	247	75	30.4
Operation with irradiation.....	350	297	161	54.2
Irradiation only.....	1,570	1,328	470	35.4
Total.....	2,179	1,872	706	37.7

\* Inquiry as of January 1, 1945. Included are only those patients operated on or treated five or more years prior to the time of inquiry; that is, 1939 or earlier. The hospital deaths are omitted from the calculations.

In considering prophylactic treatment we must consider of first importance chronic irritation from infection. It has long been considered that parity has an important bearing on cervical cancer, although statistics show that practically the same proportion of nulliparous women in the cancer age have cervical cancers as those who have had children. The important consideration, therefore, is not the treatment of the traumatic lesions of childbirth alone but the treatment of cervical infections. It has long been recognized, however, that lacerations predispose to endocervicitis and strictures; therefore, repair of such lacerations at an early date is always indicated.

Once cancer of the cervix has been diagnosed, the serious matter of advising treatment must be considered. The only methods available are radiotherapy and surgical treatment. Colloids of some of the heavy metals have been advised and there is no doubt that these have a more destructive action on malignant tissue than on normal cells; however, the curative dose is too close to the lethal dose to make their use satisfactory or dependable. The local application of caustics and extensive destruction of the local growth by cauterization are not

practical and are responsible for the formation of many fistulas but for few cures. None of the specific treatments that have been advised so far are of any value. Much experimentation along this line is being done at present and it is hoped that some day a satisfactory serum will be developed.

After a critical analysis of the results obtained in the past either by the Wertheim type of abdominal hysterectomy or by Schauta vaginal hysterectomy, taking into consideration the operative mortality rate and the expectation of life following operation as recorded by surgeons both in this country and abroad, it was not surprising that a decided change in the treatment of carcinoma of the cervix followed the discovery of radium and improvement in x-ray equipment. In most gynecologic clinics radium and deep roentgen therapy largely supplanted surgical treatment.

This change was largely to be attributed to the poor results obtained when surgical treatment was the only recognized type of treatment for all cases. One reason for the poor results of surgical treatment even in cases of operable carcinoma was that an incomplete operation was frequently done, with rapid recurrence of the malignant lesion. In other cases a radical procedure was attempted by a surgeon who was not experienced in this special type of operation and the tedious dissection of lymph nodes that is necessary, and high mortality and morbidity rates resulted. In still other cases surgical treatment was attempted in cases of hopelessly inoperable carcinoma and an incomplete operation resulted.

In recent years, following the introduction of chemotherapy and the realization of the importance of the modern methods of postoperative care, more and more surgeons are treating these patients surgically, especially by the Wertheim type of operation. If only good surgical risks in group 1 or 2 are accepted the mortality rate should not be much more than that following hysterectomy for benign conditions.

Meigs (3) reported a series of sixty-five cases of Wertheim hysterectomy without a death. Between January 1, 1943 and July 1, 1946, hysterectomy of this type was performed at the Mayo Clinic in fifty-five cases by seven surgeons. One death, from acute renal failure, occurred four days after operation. Since January 1, 1944, thirty-nine such operations have been performed without a death. Figure 1 shows the survival curves of the earlier group; namely, January, 1913, to June, 1943, inclusive. Many of the patients in this group were operated on without the benefit of modern preoperative and postoperative care. Table IV shows the hospital mortality rates in this same series for the various types of operation.

There is no doubt that efficient surgical treatment, when attempted only in suitable cases and by surgeons accustomed to the tedious dissection necessary and when combined with modern methods to protect the patients from infection and other postoperative complications, gives a relatively high percentage of cures with a very low mortality rate. When such treatment is given in conjunction with irradiation under the direction of an expert in this field of therapy, the results are so good that we feel that further trial is justified in spite of the



encouraging results obtained by irradiation alone. Table V shows the results of Wertheim hysterectomy with and without irradiation. In no other disease is it more important that all forms of treatment be carried out by specialists.

We have had practically no experience with the Taussig operation of a radical dissection of the lymph nodes and node bearing fascia without removal of the

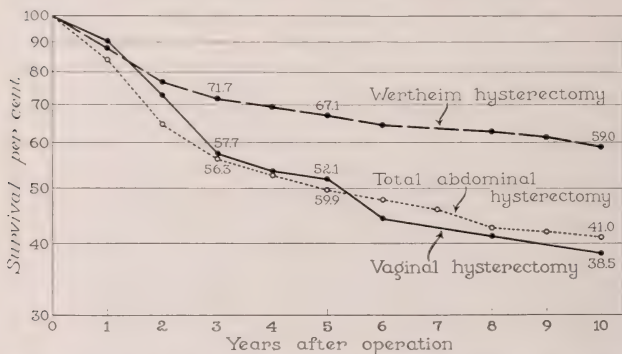


FIG. 1. Epithelioma of the cervix. Survival curves for the patients on whom the various surgical procedures were performed from January, 1913, to June, 1943, inclusive. The curves are based on 100 cases of Wertheim hysterectomy, 262 cases of total abdominal hysterectomy and 76 cases of vaginal hysterectomy. Deaths in the hospital are included in the death rate for the first year.

TABLE IV

*Hospital mortality rates following various types of surgical procedure in 438 cases of epithelioma of the cervix in which operation was performed at the Mayo Clinic from January, 1913, to June, 1943, inclusive*

OPERATION	CASES	HOSPITAL DEATHS	MORTALITY RATE, PER CENT
Wertheim.....	100	8	8.0
Total abdominal hysterectomy.....	262	6	2.3
Vaginal hysterectomy.....	76	1	1.3
Total.....	438	15	3.4

uterus but with treatment of the local lesion by radiotherapy. If the patient is a good surgical risk, however, we believe that the operation is advisable in many cases of advanced carcinoma and should be given an extensive trial.

The only surgical treatment justifiable, even for lesions of microscopic size, is a radical operation and we believe that the Wertheim technic is better than the Schauta vaginal operation. This operation should not be undertaken, however, except on patients who are good surgical risks in every sense of the word. Be-

fore attempting a Wertheim operation, it is often advisable to give one thorough course of roentgen therapy six or eight weeks prior to operation and, at the time of operation, the local lesion should be thoroughly destroyed by the actual cautery, or by what we consider a better method; namely, by thorough coagulation by the application of a saturated solution of zinc chloride and packing of the uterine cavity with a strip of gauze wrung out of the same solution. Postoperative irradiation, as we said before, should be used in all cases. Even in cases of very early carcinoma it gives an added degree of safety. Unfortunately, we learn little from reviewing statistics, as much of the surgical treatment done in the past, and unfortunately still being done, is not radical enough or is done in poorly selected cases with resulting too high morbidity and mortality rates

TABLE V  
*Results following Wertheim hysterectomy with and without irradiation*

	PATIENTS TRACED*	LIVED FIVE OR MORE YEARS AFTER OPERATION	
		Number	Per cent
Hysterectomy only.....	18	7	38.9
Hysterectomy with roentgen therapy....	40	32	80.0
Hysterectomy with radium therapy.....	1	1	100.0
Hysterectomy with roentgen and radium therapy.....	22	13	59.1
Hysterectomy only.....	18	7	38.9
Hysterectomy with irradiation.....	63	46	73.0
Total.....	81	53	65.4

\* Inquiry as of January 1, 1946. Included are only those patients operated on five or more years prior to the time of inquiry; that is, 1940 and earlier. Hospital deaths are included in the calculations.

If a hospital mortality rate cannot be kept below 5 per cent or at the outside, 7 per cent, radium and roentgen therapy should be used instead of surgical treatment in all cases.

Even if we admit that a selected group of early cervical cancers are suitable for surgical treatment if operated on by surgeons accustomed to the special type of operation indicated, we are immediately impressed with the fact that such cases are rarely seen. At the Mayo Clinic, 593 new cases of carcinoma of the cervix were encountered in the years 1930 to 1934, inclusive, but in only fifty-two (8.8 per cent) of them, was operation undertaken and, in several of these cases, the condition was found to be more extensive than preoperative examination had suggested. Besides these cases in which operation was undertaken, there were eleven cases in which the lesions were considered early and forty-four in which they were classed as borderline. In these cases treatment was by irradiation. In other words 82 per cent of carcinomas of the uterine cervix encountered at the clinic are inoperable to start with. From 1911 to 1944

inclusive, in 3,400 cases carcinoma of the cervix was treated by radiotherapy at the Mayo Clinic.

We at the clinic are not seeing cases of carcinoma of the cervix any earlier in the course of the disease than we did twenty-five years ago. The early cases are almost without exception accidentally encountered in the course of general examinations. In spite of this gloomy picture, however, the fact remains that more women are being cured of cancer of the cervix today than at any previous time. Besides the cases in which a cure was obtained, marked palliation with relief of the most distressing symptoms was obtained in the majority of cases by the judicious use of radium and roentgen therapy.

There is no doubt that progress is being made with a better understanding of the physical properties and chemical reactions of radium and roentgen rays. The surgical operations indicated for carcinoma of the cervix will probably never be improved on. If surgery is going to continue to be looked on as a justifiable form of treatment for cancer of the cervix, great care must be exercised by experienced surgeons to operate only in early cases after efficient preoperative preparation, and postoperative care should include all modern methods to combat shock, peritonitis, pulmonary complications and so forth and should be followed by radiotherapy. If this is done, probably a higher percentage of the patients can be cured than are at present.

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# A CASE OF ACUTE MYOCARDIAL INFARCTION WITHOUT ACUTE CORONARY ARTERY OCCLUSION (ACUTE CORONARY INSUFFICIENCY WITHOUT ACUTE OCCLUSION)

A. M. MASTER, M.D. AND O. AUERBACH, M.D.

[New York, N. Y.]

From the U. S. Naval Hospital, St. Albans, N. Y.

Myocardial infarction without acute coronary artery occlusion or "acute coronary insufficiency without acute occlusion" is a common disease (1-6). The diagnosis can be made on a clinical and electrocardiographic basis. It is one of the three common types of acute coronary artery diseases, namely the simple episode of angina pectoris, acute myocardial infarction without acute coronary artery occlusion and acute myocardial infarction due to acute coronary artery occlusion. They can be distinguished one from the other (2-6).

The following is a short history of a patient who suffered acute myocardial infarction without acute coronary artery occlusion and in whom the diagnosis was made before postmortem examination.

## CASE REPORT

*History.* R. J. R., a man, 37 years of age, entered the Navy in May 1943, one month after he had been rejected because of a questionable hypertension. In May 1944 he developed shortness of breath and precordial pain on slight exertion. He was admitted to the U. S. Naval Hospital, St. Albans, Long Island, September 29, 1944 with the diagnosis of coronary heart disease.

*Examination.* On physical examination the patient was of good physique, not acutely ill. The heart was of normal size and shape, the rhythm regular, and the rate 70-80 beats per minute. The second sound in the aortic region was loud. No murmurs were present. The blood pressure was 124 systolic and 94 diastolic.

*Laboratory data.* All laboratory tests were negative. The electrocardiogram (fig. 1) was abnormal. A flat T2, and inverted T3, and occasional premature ventricular beats were present.

*Course.* The patient began to improve. By October 9, 1944 the electrocardiogram had become normal. Slowly the frequency of the attacks of precordial pain diminished and soon the patient was free of them. The patient's father died suddenly in February 1945 of acute coronary artery occlusion and from that moment the patient grew steadily worse. He developed precordial pain on the slightest effort and was subject to frequent shortness of breath. On April 11, 1945 he experienced a severe attack of substernal pain, went into shock and died the next morning. The electrocardiogram (fig. 1) the day before death revealed deep depressions of the RS-T segments in the first, second and fourth leads with semi-inverted T-waves. (There were no RS-T elevations or large Q-waves.)

A definite relationship was present between the almost continuous precordial pain, the final attack of severe substernal pressure and the father's death. Because of this association of the pain to an emotional factor and the presence of the characteristic electrocardiogram, it was predicted that acute myocardial infarction due to coronary sclerosis would be discovered on post-mortem examination, but that no complete obstruction of the coronary arteries would be found that is, no acute coronary artery occlusion.

*At autopsy,* there were found congestion of the lungs, liver and other viscera due to heart failure. The heart was slightly enlarged and weighed nearly 500 grams. (The patient weighed 190 pounds.) The pericardium was smooth (fig. 2), the left ventricle increased in

size. The muscle of this chamber and of the interventricular septum was infarcted. The necrosis, even grossly, could be seen to involve chiefly the subendocardial layer. Microscopically, there were innumerable areas of necrosis and fibrosis in the subendocardial layer of the muscle. In these locations there were many collections of polymorphonuclear leukocytes and mononuclear cells.

Both coronary arteries and their branches showed advanced sclerosis, but cross-sections of these vessels serially cut, every few millimeters, disclosed no acute occlusion. Instead, the lumen was considerably narrowed, but nevertheless patent (fig. 3). The orifices of the left circumflex artery, about 3 cm. from its origin, and of the descending branch of the left coronary about 1 cm. from its beginning, were particularly small. The right coronary artery was almost as sclerotic as the left.

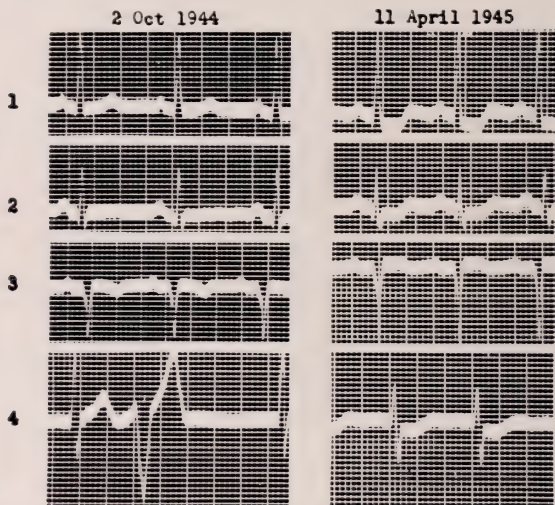


FIG. 1. The electrocardiogram of October 2, 1944 shows a heart rate of about 80/minute, a left axis deviation, a flat T2 and an inverted T3. The tracing of April 11, 1944 taken just before death, reveals extreme depressions of RS-T 1-2 and 4 with inversion of the T-waves.

#### COMMENT

There are really acute coronary artery diseases, not just one disease. In the acute arteriosclerotic group, with which this paper concerns itself, there are: 1) the ordinary episode of angina pectoris, 2) myocardial necrosis or infarction without acute coronary artery occlusion or thrombosis, and 3) acute myocardial infarction due to acute coronary artery occlusion or thrombosis. These three diseases are arranged actually in the order of their severity.

In the simple anginal syndrome, the chest pain is momentary, definitely related to effort, excitement, ingestion of food, cold and relieved by nitroglycerine placed



under the tongue. No nausea or vomiting occur. There are no cardiovascular phenomena except perhaps a rise in blood pressure during the attack and ephemeral RS-T segment depressions with T-wave inversions. Other laboratory tests are negative.



FIG. 2. Pericardium is intact, smooth and glistening.

Passing over to the last type of acute coronary artery disease, namely acute myocardial infarction due to acute coronary artery occlusion or simply "acute coronary occlusion," we find the extreme opposite, clinically and pathologically. This is a complete closure of a coronary artery, the sequel to advanced arteriosclerosis. The event is not related to exertion or emotion. The pain is substernal, severe, not relieved, but rather aggravated, by nitroglycerine. Gastro-intestinal disturbances, and cardiovascular reactions are present. Nausea, vomiting, shock, fall in blood pressure, poor heart sounds and gallop rhythm, leukocytosis, increased temperature, fast sedimentation rate and a specific

electrocardiogram are observed. Elevations of the RS-T segment which progress to inverted T-waves, and large Q-waves are present. The infarct is large, involves the pericardium (producing a rub) and the endocardium (causing mural thrombosis and embolization). The coronary artery is completely closed.

The type of acute coronary artery disease under discussion, that is, acute myocardial infarction without acute coronary artery occlusion or simply, "acute coronary artery insufficiency," is intermediate between the ordinary bout of angina pectoris and the complete acute closure of a coronary vessel. The pain may be severe and prolonged; the attack is related to physical effort, excitement, cold. The clinical and laboratory observations may be those discovered in acute

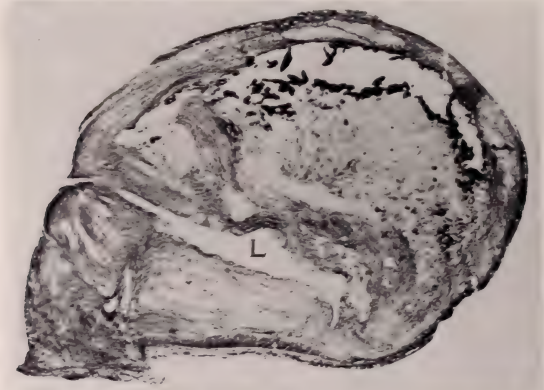


FIG. 3. Photomicrograph of the circumflex branch of the left coronary artery near its origin. The lumen (L) is narrowed by arterio-sclerotic plaques, but it is definitely patent. The endothelial lining of the lumen is complete. The intima is thickened but there are no intimal or subintimal hemorrhages. Cholesterol crystals and calcium deposits (black) are present in the plaques.

coronary artery occlusion but usually not as severe. In other words, only in serious conditions may there be prolonged pain, shock, change in heart sounds, fall of blood pressure, fever, white blood cell increase and even a fast sedimentation rate. The electrocardiogram is characteristic and differs sharply from that in acute coronary artery occlusion. RS-T depressions with T-wave inversions are obvious but no RS-T elevations and no large Q-waves. This form of the electrocardiogram is undoubtedly related to the peculiar characteristics of the pathological changes in the heart muscle. The latter usually contains many diffuse areas of subendocardial necrosis, often in the papillary muscles but not involving the endocardium or pericardium.

"Acute coronary insufficiency" has now been established as a complete entity (3-6). It is a definite form of acute coronary disease, as distinct as acute

coronary occlusion. Acute coronary insufficiency has its predisposing and precipitating factors; it produces a transient functional anoxia, or if this is prolonged, actual necrosis of the subendocardial and papillary regions of the left ventricle. As a result of this anoxia, RS-T segment depressions and T-wave inversions appear in the electrocardiogram. Finally, therapeutic measures in this dysfunction are determined by the predisposing and precipitating agents: transfusions for acute hemorrhage; digitalis for heart failure and tachycardia; prevention of anoxemia of any cause by an adequate supply of oxygen during operation; and care for shock. Avoidance of overexertion in severe coronary disease needs no emphasis.

#### SUMMARY

A case of acute myocardial infarction without acute coronary artery occlusion is described. The diagnosis can be made on clinical grounds and the characteristic electrocardiogram. Like the simple episode of angina pectoris, but unlike acute myocardial infarction due to acute coronary artery occlusion, the attack is precipitated by effort and emotion. The electrocardiogram presents depressions of the RS-T segments with T-wave inversions, no RS-T elevations, no large Q-waves. This characteristic electrocardiogram is associated with the definite pathological picture of subendocardial necrosis without involvement of pericardium and endocardium.

There are many acute coronary artery diseases, namely the simple attack of angina pectoris, acute myocardial infarction without acute coronary artery occlusion (acute coronary artery insufficiency without acute occlusion) and finally myocardial infarction due to acute coronary artery occlusion (acute coronary artery insufficiency with acute coronary occlusion).

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## RELATIONS BETWEEN DEPRESSED RESPIRATORY METABOLISM AND LOW FERTILITY\*

SAMUEL R. MEAKER, M.D.

[*Boston, Mass.*]

It is customary to accept as normal all basal metabolic rates between 10 per cent below and 10 per cent above the predicted figure, presumably because findings within that range suffice to rule out myxedema on the one hand and thyrotoxicosis on the other. Some practitioners feel that rates lower than  $-10$  have little clinical import unless accompanied by conspicuous evidence of endocrine disturbance. But as a matter of fact, careful observation of patients whose respiratory metabolic levels fall within the so-called low normal range reveals a rather frequent incidence of symptoms attributable to functional depression. Among these are fatigability, lack of energy, sensitiveness to cold, constipation, diminished libido, and menstrual disorders. This paper will consider possible cause-and-effect relationships between hypometabolism and infertility.

In a consecutive series of 100 sterile matings studied by my group<sup>1</sup> and not previously reported, the average basal metabolic rates were  $-7.19$  for the husbands and  $-5.68$  for the wives. Table I shows the distribution. It is significant that of the 200 patients 154 had rates on the minus side, while in 66 the rates were under  $-10$ , the conventional low normal limit. All determinations were performed by trained technicians who did their best to obtain accurate results. Nevertheless, our readings are undoubtedly too high, since the majority of the patients were undergoing the test for the first time and it is difficult to insure a truly basal state in unconditioned individuals.

### HYPOMETABOLISM AND SPERMATOGENESIS

Four cases of azoöspemia were encountered in this series, of which two resulted from a profound depression of spermatogenesis, one from bilateral epididymal blockade, and one from atrophy due to old mumps orchitis. A fifth husband was prevented by psychic inhibitions from contributing a seminal specimen, though he had no difficulty in delivering normal spermatozoa to his wife's endocervix. Thus 95 semens became available for quantitative evaluation, the results of which are set forth in Table II. In nearly every case the figures given represent the average of two specimens produced several days apart.

It is difficult to define normal standards for semen, since great variations are encountered among clinically fertile men. In practice the personal experience of each investigator will determine the borderlines which he accepts. Vose and I have always viewed with suspicion specimens having counts under 60,000,000

\* From the Department of Gynecology of the Boston University School of Medicine, and the Gynecologic Service of the Massachusetts Memorial Hospitals.

<sup>1</sup> All of the urologic examinations and semen studies were carried out by Dr. Samuel N. Vose. Most of the medical-endocrine investigations were made either by the late Dr. Charles H. Lawrence or by Dr. John J. Curry.

per cubic centimeter, or initial motility of less than 70 per cent, or no motility at the end of 24 hours, or more than 25 per cent of abnormal forms according to our

TABLE I  
*Basal metabolic rates in 100 unselected sterile couples*

NUMBER OF HUSBANDS	B.M.R.	NUMBER OF WIVES	NUMBER OF HUSBANDS	B.M.R.	NUMBER OF WIVES	NUMBER OF HUSBANDS	B.M.R.	NUMBER OF WIVES
2	+13	1	3	-1	1	4	-11	6
1	+11	1	1	-2	4	5	-12	3
2	+10	1	7	-3	10	3	-13	5
2	+9	2	4	-4	2	7	-14	2
1	+8	1	5	-5	3	7	-15	4
2	+7	2	5	-6	1	1	-16	2
4	+6	3	3	-7	2	1	-17	3
2	+5	5	10	-8	4	3	-18	1
1	+4	1	7	-9	8		-19	1
2	+3	3	3	-10	5	2	-20	2
1	+2	3					-25	1
2	+1	2				1	-26	
2	0	4				1	-29	
							-30	1
17		29	48		40	35		31

TABLE II  
*Relation of basal metabolic rate to values of sperm population*

BASAL METABOLIC RATE	SPERMATOZOA											
	Millions per cubic centimeter						Percentage Motile			Percentage of abnormal forms		
	151 or more	150-100	100-61	60-31	30-11	10 or less	71 or more	70-21	20 or less	25 or less	26-33	34 or more
+11 to 0 15 cases.....	3	5	4	2	0	1	9	1	5	6	4	5
Average .....	102.467						54			29.7		
-1 to -10 46 cases.....	6	9	16	7	5	3	24	10	12	14	23	9
Average .....	83.848						54			28.8		
-11 to -29 34 cases.....	7	9	5	3	5	5	21	2	11	10	19	5
Average .....	89.441						55			29.5		

morphologic criteria. We feel, however, that a deficiency in one feature is sometimes counterbalanced by excellence in others, and in particular that counts considerably lower than 60,000,000 may be consistent with good fertility pro-



vided that motility and morphology are satisfactory. Furthermore one must take into consideration the volume of the ejaculate and the viscosity of the seminal fluid. The final assay depends upon a judicious weighing of all these data, special importance being attached to the item of morphology. When a semen is graded as good, fair, or poor by an over-all survey of this sort, the result probably gives the most accurate idea of its true worth that can be obtained. Table III shows how ratings thus assigned correlate with metabolic levels in 95 men of our series.

These observations make it apparent that hypometabolism has no constant or specific effect on the commonly studied biologic properties of spermatozoa. Some of the best seminal specimens were produced by men whose metabolic rates were among the lowest. Hamblen, Pullen and Cuyler (1) have reported similar findings. The conclusion is that depressed respiratory metabolism does not

TABLE III  
*Relation of semen assay to basal metabolic rate*

SEMEN		BASAL METABOLIC RATE		
		+11 to 0	-1 to -10	-11 to -29
good	32 cases 100%	6 cases 19%	14 cases 44%	12 cases 37%
fair	35 cases 100%	3 cases 9%	20 cases 57%	12 cases 34%
poor	28 cases 100%	6 cases 21%	12 cases 43%	10 cases 36%

necessarily interfere, at least in any way demonstrable by ordinary methods of examination, either with the gonadotropic action of the anterior pituitary or with the reactivity of the male germinal epithelium.

#### HYPOMETABOLISM AND OVULATION

To obtain evidence on ovulation we use vaginal smears, hormone assays, and basal temperature curves in selected cases, as well as mid-cycle symptoms whenever the patient can report them. Endometrial biopsy is a routine item in our sterility study. Circumstances, most often unpredictable cycles, prevented the obtaining of premenstrual biopsies in 12 cases of this series. Of the 88 biopsies taken either just before the flow or during the first few hours, 63 showed a normal progestational endometrium, while in 25 there was one type or another of non-physiologic response. Table IV gives the relationship of normal and depressed metabolic rates to these findings. Incidentally it might be mentioned that no tuberculosis was encountered; there occurred, however, one entirely unsuspected case of adenocarcinoma.

Again our observations confirm those of Hamblen, Pullen, and Cuyler (2). In so far as a progestational endometrium may be accepted as an index of ovulation,

these data suggest that the level of respiratory metabolism commonly has no influence on oögenesis, and likewise none on endometrial responses to ovarian stimuli, unless it be that metabolic rates on the minus side are slightly more favorable.

TABLE IV  
*Relation of basal metabolic rate to endometrial biopsy findings*

BASAL METABOLIC RATE	BIOPSY FINDINGS	
	Normal	Abnormal
+13 to 0		2 no progesterone effect 4 subnormal progesterone effect 3 mixed effect, progesterone and excess estrin 1 atrophy
25 cases 100%	15 cases 60%	10 cases 40%
-1 to -10		6 no progesterone effect 1 subnormal progesterone effect
36 cases 100%	29 cases 81%	7 cases 19%
-11 to -30		3 no progesterone effect 3 subnormal progesterone effect 2 mixed effect, progesterone and excess estrin
27 cases 100%	19 cases 70%	8 cases 30%
Total 88 cases 100%	63 cases 72%	25 cases 28%
Average B.M.R.	-6.14	-5.04

#### HYPOMETABOLISM AND MENSTRUATION

There is frequent association between abnormal metabolic levels and menstrual disorders, though no constant relationship can be defined. The high rates of thyrotoxicosis may be accompanied either by too much flowing or by too little, and the same is true of the various conditions in which metabolism is depressed.

Of the 100 wives in this series 71 reported normal menstrual behavior. Among the 29 others, 21 had prolonged cycles, two short cycles, two cycles irregularly long or short, three scanty flow, and one excessive flow.

The average metabolic rates were -4.82 for patients menstruating normally, and -7.79 for the abnormal group. While no definite correlation can be established between these figures and fertility levels, the general indication is one of parallelism between metabolic depression and poor functioning of the female reproductive apparatus.

## HYPOMETABOLISM AND INHERENT FERTILITY

From time to time one hears of sterile couples in whom their physicians have not been able to find anything wrong. Such a report always means incomplete diagnostic study. My co-workers and I have never seen a case in which careful investigation failed to reveal at least two factors potentially inimical to fertility.

It is, nevertheless, true that a certain number of couples present no conspicuous and serious hindrance to conception. The semen is at least fairly good; spermatozoa arrive safely in the endocervix, where the secretions are not markedly hostile; there is no high-grade tubal obstruction; and as far as can be judged, ovulation occurs. In other words, the sum-total of obstacles does not appear unsurmountable, and yet pregnancy fails to occur.

One may reasonably assume that in this group of cases the inherent or intrinsic fertility of the gametes is somewhat lower than in the general run of sterile matings. The question arises whether depressed oxygen metabolism has special importance as a contributory cause. Fifty of our 100 couples may be regarded as belonging in the category above defined. The average metabolic rate of the husbands was  $-7.2$ , practically the same as the figure for the entire series. The average rate of the wives was  $-6.86$ , as compared with  $-5.68$  in the series as a whole.

Since serious local impediments to fertility are much commoner in the genital organs of women than in those of men, and since both sexes are equally subject to constitutional depressions, it is to be expected that in the restricted group of cases under consideration an increased incidence of all sorts of constitutional factors will manifest itself more notably on the female side. As to hypometabolism, our figures are less striking than they might prove to be in a larger series; but at least they suggest that in women the incidence of this condition tends to parallel that of other depressed constitutional states in the causation of low inherent fertility.

## SIGNIFICANCE OF HYPOMETABOLISM

The figures of Table I, together with similar observations made by other workers, prove that an association of some sort exists between subnormal respiratory metabolism and infertility. The fact that frequent cures of sterility are obtained when low metabolic rates are raised proves, as Litzenberg (3) has well expressed it, that hypometabolism is "a cause (or index of a cause)" of poor reproductive performance. Two questions present themselves. First, what is the genesis of the metabolic depression so often encountered in clinical cases of sterility? And second, in what way does this depression (or the cause of which it is an index) operate to interfere with conception, as well as with the normal continuation of pregnancy?

It would be a mistake to assume that depressed respiratory metabolism always denotes thyroid insufficiency. A small proportion of healthy people have naturally low metabolic rates, just as some have slow pulses, low blood-pressures, or subnormal temperatures. Metabolic depression may result from the severer grades of hypopituitarism or hypogonadism in either sex, and from various non-endocrine disorders such as malnutrition or anemia.

It is, on the other hand, a mistake to assume that low metabolism cannot be due to thyroid insufficiency unless the patient presents a frank picture of myxedema, or at least evidences strongly suggestive of that disease. This idea discounts the fact that most functional disorders occur in a wide range of grades and degrees. The mildest usually escape recognition; those slightly more pronounced are likely to be overlooked by clinicians not alert to the possible significance of inconspicuous signs and symptoms. Subclinical hypothyroidism is now recognized as a definite entity. And furthermore, as Lawrence and Rowe (4) have shown, there is one type of thyroid failure which, even in its more severe degrees, does not produce anything resembling the classical myxedematous status.

Of sterility patients with hypometabolism only a small minority show disorders of glands other than the thyroid, or non-endocrine disturbances, severe enough to explain their metabolic depression. The majority tolerate thyroid therapy well even in fairly large dosage, and under such treatment many report relief of various minor symptoms as well as an improvement in general well-being. Thus it seems reasonable to conclude that the low metabolic rates of these patients indicate a mild degree of true hypothyroidism.

The question then comes up as to how hypothyroidism acts to depress fertility. Functional interrelations between the thyroid and the pituitary-gonad axis are ill understood. There is no necessary correspondence: thyrotoxic patients tend to be infertile, while occasional myxedemics succeed in reproducing. Hypothyroidism sometimes leads to obvious ovarian failure, evidenced by non-ovulation and amenorrhoea; it is uncertain whether the ovarian malfunction in such cases is a primary effect, or secondary to a pituitary depression. Similarly, though less often, hypothyroidism may result in male hypogonadism or in poor spermatogenesis.

But, as has been shown, most patients with low metabolic rates produce apparently satisfactory spermatozoa or ova. Evidently these gametes lack some sort of vital spark, some undemonstrable quality necessary for good fertility. The explanation of their inadequacy may well lie in the effects of a depressed oxygen metabolism on the germ plasm, and in the present state of knowledge on the subject this seems the most plausible hypothesis.

#### THYROID THERAPY IN STERILITY

In view of the evidence showing that an active respiratory metabolism is essential to optimal fertility, and that degrees of hypometabolism unimportant in other respects may create a considerable impediment to reproduction, my associates and I aim to maintain the basal metabolic rates of all sterility patients, male and female, at or slightly above the +10 level. Except in the relatively few cases where other methods are indicated, we use the carefully controlled administration of desiccated thyroid for this purpose. It is a question academic rather than practical whether the good results of this treatment are due to specific replacement, as we believe, or to the pharmacodynamic action of thyroid substance as a general stimulant of metabolic activity.

The proper regulation of thyroid therapy requires close supervision. According to the metabolic level in each case an initial dose is prescribed, which may well be two grains of desiccated thyroid U. S. P. a day for all patients whose rates are below  $-10$ , and one grain for those with rates from  $-10$  to  $+5$ . At the end of a month another metabolism test, usually more reliable than the first, and a survey of symptoms indicate what adjustment of the dosage is advisable; most often this will be on the side of increase. A similar check-up is carried out at monthly intervals until one determines the maintenance ration sufficient to keep the patient in equilibrium at the desired level, or as close to it as is possible without producing untoward effects. Some individuals begin to show symptoms of intolerance at metabolic levels lower than  $+10$ . In no case should treatment be pushed to the point of causing tachycardia, palpitation, nervousness, tremor, headache, diarrhoea, or undue loss of weight. If pregnancy occurs the wife continues to take thyroid, as a preventive measure against abortion, in gradually decreasing dosage.

Litzenberg (5) states that in 15 years of experience he obtained a consistent 30 per cent of pregnancies from thyroid therapy of hypometabolism in women. Of 36 hypothyroid wives treated by Nicodemus and Ritmuller (6), 19 conceived. Many other workers have had results almost as good. Reports on the male are fewer, and in general less impressive. The reason for this is undoubtedly that most urologists do not make a routine practice of determining metabolic rates and correcting relatively mild depressions in cases where the semen is apparently satisfactory. Thus they overlook innumerable opportunities of improving male fertility. Hamblen (7) attributes ten per cent of his cures of sterility to thyroid treatment of wives and five per cent to similar treatment of husbands.

As to our own experience, we estimate that in our successful cases the administration of thyroid has played an important part in the treatment of about ten per cent of the wives and of somewhat more than ten per cent of the husbands. But our routine diagnostic study identifies several possible causative factors of infertility in nearly every couple examined, and as a rule we attack most if not all of these simultaneously. For that reason it is difficult to evaluate accurately the benefit produced by any single therapeutic measure. Of the 100 cases reported in this paper, only one was treated by thyroid alone. The wife's basal metabolic rate was  $-30$ , the lowest in the series, and the husband's  $-15$ . When both rates were raised into the plus range conception promptly occurred, and the wife is now approaching the end of a normal pregnancy.

#### SUMMARY

Low respiratory metabolic levels occur with notable frequency in men and women whose matings are involuntarily sterile. The cause of most of these depressions is probably a mild degree of hypothyroidism. Their usual effect is not to interfere with gametogenesis in any obvious way, but rather to diminish the essential fertility of the spermatozoa and ova.

Reliable determinations of the basal metabolic rates of both husband and wife are indispensable items in a complete sterility study. They should never be



omitted on the ground, for example, that the patient shows no suggestion of endocrine disorder, or that the semen appears excellent, or that endometrial biopsy-findings are satisfactory.

If low rates are systematically raised by thyroid therapy to the upper limit of the so-called normal range, the result will be a gratifying number of cures of sterility unobtainable by other means.

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## THE FASCIAL SLING OPERATION FOR INCONTINENCE OF URINE

JOE VINCENT MEIGS, M.D.

(Boston, Mass.)

There has always been a good deal of dissatisfaction with the results of the surgical treatment of stress or strain incontinence of urine in women. The Kelly operation and the Kennedy operation are fairly satisfactory and produce cures in some patients but not in others. It is noticeable that some are cured for a few months and some for years, but that after a lapse of time the same symptoms occasionally recur. Certainly no operation devised for the relief of incontinence is 100 per cent perfect and the interest in the problem is great, not because this type of lesion is dangerous but because there is nothing much more disagreeable than being wet and never being sure when a cough or sneeze will cause a momentary loss of control. It is a very simple but very disagreeable defect. The cure of it would seem to be easy. Suture the sphincter muscles of the urethra tighter and all should be well. In many cases this is true but there are some whose relief is not at all simple and various methods have been tried to cure them. Perhaps the cure is linked up with the anatomical position of the urethra rather than the sphincter muscles. In the normal female, who has had no children, the urethra can be distinctly felt and can be rolled under the examining finger. The urethra under the symphysis and its orifice at its distal end points directly outward when the patient is in lithotomy position. In many multiparous patients the urethra is flattened out; it is loosened and it more or less points toward the ceiling. Not all patients with such a urethra have incontinence. Under certain circumstances, such as a full bladder and a sudden laughter or cough, a few drops will be expressed. These patients do not complain of incontinence but they are early examples of the ones who do complain. It is also true that some nulliparae are not absolutely continent. However it is obvious to those of us interested in the problem that in nearly all cases of true stress incontinence the urethra is flattened and the urethra points anteriorly. Often, though not always, there is a bulge of the urethra or "urethrocele" but more often, a bulging of the anterior vaginal wall or "cystocele." Sometimes the anterior vaginal wall when observed in the lithotomy position is straight up and down and the urethra cannot be seen on inspection. The usual operation to cure incontinence reconstructs the urethra, the tissues are tightened around it, the bladder or vagina "fascia" is isolated and brought together, and the urethra is replaced under the symphysis. *It is probable that the anatomical replacement cures the patient of her incontinence.* Reconstruction of the external striated sphincter muscle of the urethra does not of itself cure the incontinence. In doing such operations I have never seen tissue that I believe to be striated muscle in the region of the anatomical urogenital diaphragm. In patients with incontinence this muscle and the inferior and superior fascial layers are not visible as distinct layers. Reconstruction is at best guess work and luck.

In considering the problem of incontinence it occurred to me that the most important reconstruction was to replace the urethra in its normal position, that of starting from the bladder behind the symphysis and pointing straight out. Very gentle pressure on the posterior urethra with the examining finger prevents leaking on laughing, acting perhaps as the prostate does in the male. Thick scar tissue therefore in this region about the urethra might help in the cure. The latter was suggested by the work of Murless who advocated the use of a sclerosing solution underneath and around the urethra. Dr. Marshall K. Bartlett of our Gynecologic Service, who has done a series of Kennedy operations, has tried this method in those patients in whom it had failed and it has worked successfully in one of these. Therefore it occurred to me that correct position of the bladder and urethra, elongation of the urethra, slight pressure on the posterior urethra, and increase in density of the tissue about the urethra might be all that was necessary to cure this disagreeable defect. The operation of fascial sling repair to be described in this paper was completely thought out and plans were about to try it when Dr. Aldridge's article appeared in the *American Journal of Obstetrics and Gynecology* in 1942. Dr. Aldridge's operation consists of suturing transverse strips of abdominal fascia beneath the urethra. He develops the rectus and external oblique fascia from above and pulls the fascia down under the symphysis from below and sutures it under the urethra. This operation accomplishes the same purpose that I had in developing the so-called fascial sling operation. Shortly after Aldridge's article was published the first case was operated upon and the first three patients so operated upon had very satisfactory results. Two of these have been followed over 35 months and one over 11 months, and two of the end results are considered excellent and one as good. It was felt that it was unwise to report this operative procedure until considerable experience had been had with it and until a satisfactory follow-up proved that the results were lasting. It is my belief that this operation and the Aldridge operation accomplish the same thing, the only difference being that the fascial sling operation pulls the urethra up higher and that there is no break in the continuity of the fascia. Kennedy's latest paper discussing the voluntary muscle of micturition and the internal sphincter is the result of an excellent anatomical investigation and describes in detail the muscles and how they function. His conclusions demonstrate that it is the restoration of the position of the bladder and urethra that is of greatest importance. This is best accomplished by infolding the smooth muscles<sup>1</sup> of the bladder and urethra and by tightening the smooth muscle

<sup>1</sup> There is no doubt that Byron H. Goff is correct when he says there is no real fascia under the vaginal mucous membrane or under the mucosa of the bladder. What is generally considered as "fascia" is smooth muscle. Encouraged by the definiteness of Goff and of Inglis F. Frost, areas of so-called fascia have been examined in our Laboratory and have been pronounced as smooth muscle. Goff's article (*Surgery, Gynecology, and Obstetrics*, 52: 32, 1931) is undoubtedly correct and gynecologists the world over make a mistake in calling the tough fibrous structures fascia when in reality they are smooth muscle. Between the layers of smooth muscle there is an areolar fascia but it is too thin to use as a support or to suture. At its lateral insertion this areolar fascia becomes the fascia endopelvina. In trying to obtain the proper cleavage plane the technique followed by the gynecologists of the Woman's Hospital of New York should be followed.

and mucous membrane of the anterior vaginal wall. Complete restoration is more perfectly accomplished by means of a fascial sling.<sup>2</sup> By this means the urethra is elongated, an important part in the cure of incontinence. Proper restoration of position allows proper resumption of function.

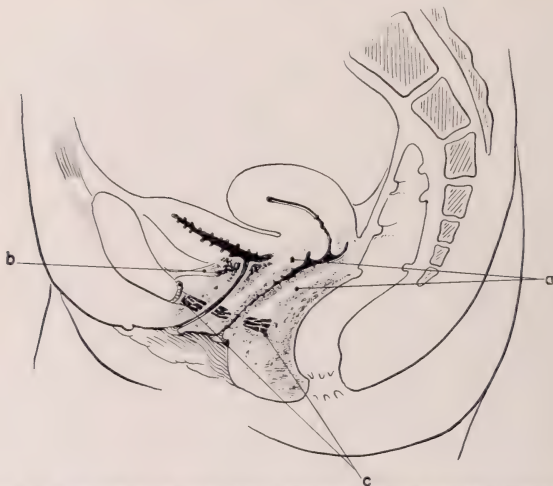


FIG. 1. a. The "fascia" or bands of smooth muscle that course about the vagina are illustrated in white. Upon the proper position of this tissue depends the position of the bladder and upper urethra. A stretching of the anterior vaginal wall will permit a sagging of the urethra and neck of the bladder.

b. This shows the suspensory ligamentous support of the roof of the urethra. This is a fixed and rarely disturbed area.

c. Shows the urogenital diaphragm starting at the symphysis and ending in the perineum. This diaphragm contains between its two fascial layers the sphincter muscle of the membranous urethra. This drawing is greatly exaggerated and such a division of inferior layer of fascia, muscle, and superior layer of fascia is never seen. The repair of the external sphincter is usually impossible. (After drawings in Atlas and Textbook of Human Anatomy by Johannes Sobotta and J. Playfair McMurich, Philadelphia, W. B. Saunders, 1914.)

#### ANATOMY AND PHYSIOLOGY OF THE BLADDER AND THE URETHRA

There has been an enormous amount of investigation into the reason for the control of urination or continence. As far as this paper is concerned the problem will be simplified as much as possible and an interpretation of the functions of muscles and fascias involved will be presented.

<sup>2</sup> This sling operation is credited by TeLinde in his book "Operative Gynecology" to Goebell, Frangenheim, and Stoekel. This paper was written before the publication of TeLinde's book and the author was not cognizant of the fact that this operation had been suggested and performed by three eminent European gynecologists. The idea was original to the author and no knowledge of its previous use and description was known to him.

First it is obvious to me that the urogenital diaphragm made up of the voluntary sphincter of the urethra encased between two layers of fascia is a very difficult piece of anatomy to visualize in patients with incontinence and, I feel sure, extremely difficult to utilize. In Figure 1 the position of the external or voluntary sphincter of the urethra indicates how difficult it would be to use it. It is not in the same plane as the anterior vaginal wall with its smooth muscle, which is so important to utilize in the relief of cystocele and incontinence. The urogenital diaphragm is that firm area of tissue just below the urethra which is reached after the anterior vaginal wall has been dissected from the bladder. The lines of cleavage between the vagina and the bladder are very clear cut because the bladder, its neck, and trigone probably move somewhat during filling and emptying of the bladder. This dissection is easily made with gauze or by opening and shutting the scissors but near the upper part of the dissection, just below the urethra, a dense fascial tissue is encountered that the scissor method will not separate. This is the area of the urethral perforation of the urogenital diaphragm. The inferior and superior layers of fascia and the sphincter muscle of the urethra are supposed to be separate entities but are practically inseparable. Perhaps in the virgin this separation can be made but in women who have had children it seems to be impossible. Occasionally there is sufficient tissue here to place a stitch to decrease the diameter of the urethra and possibly if there is muscle present the voluntary muscle of the urethra will be reinforced. It is doubtful if the muscle is of any great value in the control of the bladder and urethra. It is the involuntary muscles that are important and they are at the neck of the bladder and in its trigone. Surely one coughs in one's sleep and it is *not* the voluntary muscle that keeps the urine back; it is the automatic function of the internal sphincter that does it. It is to be greatly doubted if the voluntary sphincter of the membranous urethra is important in the cure of incontinence.

Injury to and stretching of the anterior vaginal wall is the most important abnormality in patients with incontinence. Why is this so? Because if the anterior vaginal wall sags the bottom of the neck of the bladder and the posterior wall of the urethra which are ordinarily perfectly well suspended to the back of the symphysis and represent a fixed point must have been loosened (fig. 2). This fascial suspension of the urethra and bladder can be easily seen when performing the abdominal part of the sling operation. The anterior bladder and anterior urethra remain suspended in prolapse of the urethra and cystocele while the posterior wall, trigone, and posterior urethra follow the sagging anterior vaginal wall. The internal urethral orifice is pulled open and stretched and this prevents the weak, automatic sphincter of the bladder neck from functioning from its fixed point behind the symphysis. (Kennedy's "muscle of micturition" must also be stretched.) If, however, at operation the anterior vaginal wall is pushed up and its smooth muscle jointed together beneath the bladder the urethral orifice is in perfect anatomical position again and the sphincter muscle regains its tone. The pull is in the proper direction and the fixed point restored and thus continence is re-established. It is very important that the anterior vaginal wall is replaced.



The stretched muscle of the bladder sphinctre regains its tone and function is restored.

Careful inspection of Figure 2 will demonstrate that if the anterior vaginal wall sags, the floor of the bladder and the floor of the urethra fall with it and open the internal urethral orifice and the neck of the bladder. If the ligaments of the posterior part of the symphysis which hold and fix the bladder neck and urethra

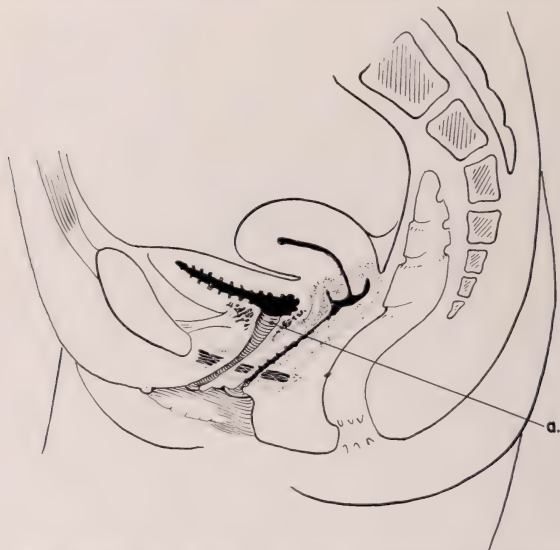


FIG. 2. Here the "fascia" or smooth muscle layer of the anterior vaginal wall has sagged and has allowed the internal sphincter or bladder orifice to open and stretch. Repair of the open sphincter, the real cause of incontinence, depends upon repair of the anterior vaginal wall. For with proper support the sphincter will regain its tone and proper function will be restored. The ligamentous support of the roof of the urethra is undisturbed. (After drawings in *Atlas and Textbook of Human Anatomy* by Johannes Sobotta and J. Playfair McMurrich, Philadelphia, W. B. Saunders, 1914.)

are injured the whole anatomy of the bladder is upset and the muscle control interfered with because of a lack of a fixed point. The smooth muscle of the bladder and the smooth muscle of the vagina are separated on the anterior wall of the vagina by a very thin areolar tissue.<sup>3</sup> There can be no heavy fascia surrounding the whole bladder for in that case the bladder could not stretch. The smooth muscle of the bladder surrounds it and is carried to the urethra as it penetrates the urogenital diaphragm. This smooth muscle, if it is not stretched

<sup>3</sup> See footnote 1 on page 505.

or injured, gives the bladder tone and support and keeps the internal sphincter in its proper position. The smooth muscle of the vaginal wall, called fascia in most instances, also depends upon its tone for the proper position of the anterior vaginal wall and if it is stretched and the bladder muscle is stretched then the internal sphincter is opened and incontinence develops. The smooth muscle of the vagina is attached laterally and does not envelop the bladder. It is the support or diaphragm of the bladder. If the wrong line of cleavage is entered then the vaginal smooth muscle is followed to its lateral insertion and thus the bladder smooth muscle is not exposed and therefore cannot be utilized if infolding of the bladder is considered wise. Laterally, the areolar fascia becomes the fascia endopelvina and is a stout structure but it can't be used as a bladder support as it is too far lateral. The bladder and vaginal smooth muscle inserting as they do at the symphysis and into the urogenital diaphragm support the bladder and its trigone from symphysis to cervix. It is very easy, when the dissection is carried laterally far enough, to place the finger up behind the symphysis from below. This is because if the proper cleavage plane has been found the smooth muscle of the bladder and the smooth muscle of the vagina separate in this region. Thus it is easy to go through the areolar fascia which separates the two smooth muscles. Imbrication of the smooth muscle wall of the bladder at this region probably helps to pucker up the internal sphincter muscle, and tightening of the anterior vaginal wall muscle and mucous membrane gives a tight anterior vaginal wall and proper support to the bladder that rests upon it. Infolding the bladder and tightening of the vagina cures the cystocele or urethrocele or both and this allows the internal sphincter muscle to regain its tone. This helps to pull the urethra and bladder neck high up behind the symphysis. The anterior vaginal wall must be reconstructed as high up upon the urethra as possible for a sagging urethra interferes with normal function.

When doing a total hysterectomy it will be noted that the "fascia" surrounding the cervix is a continuation of the anterior vaginal wall smooth muscle. It is tough and fibrous and microscopically contains connective tissue and smooth muscle and it is easily demonstrated during this operation that the bladder lies upon it. As the bladder is pushed further and further down in the radical operation for cancer of the cervix no other layer is recognized under the bladder until the urogenital diaphragm is reached. In my opinion the smooth muscle of the bladder and the smooth muscle of the vagina are separated by a thin areolar fascia and these two muscle layers must be in their proper positions to have continence of urine.

It is sometimes noticed in performing a total abdominal hysterectomy when the vagina is pulled up tight from inside the abdomen that the position of the urethra is restored and that a mild incontinence of urine is cured. This is explained because the anterior vaginal wall is shortened by removal of the cervix and tightened by repair of the vagina from the inside, restoring a proper anterior vaginal wall. This bears out the previous explanation for cure of incontinence by anatomical reconstruction. Incontinence is not due to direct muscle and nerve injury but is muscle and nerve injury due to lack of proper position.

As mentioned above it is common knowledge that very little pressure is needed to stop extreme stress incontinence by pressing on the anterior urethral wall from below. The fascial sling placed beneath the urethra acts as the examining finger does when pressing from below upon the urethra. The fascial strip gives this pressure, aiding in the cure of incontinence not only by the pressure but also by correcting the normal anatomy of the neck of the bladder and the trigone. The trigone muscle which pulls open the internal orifice cannot work if it has no fixed point to work against. Restoration of function comes with restoration of anatomy. It is the strength of the anterior vaginal wall and the proper position of the urethra with a definite fixed point that cures incontinence.

#### THE OPERATION

This operation was first done on February 9, 1943 at the Pondville Hospital (Massachusetts Department of Public Health). It was first discussed in the discussion of Studdiford's paper on the Aldridge operation at a meeting of the New York Obstetrical Society on December 14, 1943. It was next discussed, after a number of cases had been operated upon, at a meeting of the Boston Obstetrical Society on March 21, 1944, in the discussion of Aldridge's paper on incontinence. It was considered unwise to report the operation until sufficient time had elapsed to prove its value.

The operation is not difficult but its development presented certain problems. In the first three cases, done within a month of each other, it was noted how difficult it was to release the urethra from the anterior vaginal wall from above. Blunt dissection lifted the urethra with a great deal of difficulty and finally in one patient the gloved finger went through the bladder from one side to the other. (This patient has a 100 per cent cure due probably to scar tissue formed by the trauma and to the fact that the anterior vaginal wall was tightened by the total hysterectomy that was done at the same time.) It was next decided and discussed in New York in December, 1943 that it might be more satisfactory if an operation of the Kennedy type was done below, before doing the sling operation above. In all but the first three cases this plan was carried out and the operation is now much easier in its execution. The anterior vaginal wall is opened, the bladder and vaginal wall are separated as far laterally as possible. The finger is then placed through the open area on either side of the urethra and carried up behind the symphysis. The smooth muscle of the bladder is infolded and the smooth muscle of the vaginal wall and the mucous membrane of the vagina trimmed and closed. A Foley catheter is placed in the bladder from below at the time of the vaginal part of the operation and left in place to facilitate locating the urethra from above. To aid in finding the opening under the urethra from above a thin strip of gauze, as suggested to me in a letter from Aldridge, or rubber wick should be placed in each of the openings behind the symphysis around the urethra before closing the vagina. The gauze or rubber can then be found from above and the fascial strip sutured to one end and thus easily pulled through and under the urethra (fig. 3).

A practical point in opening the area behind the symphysis is to remember

that the fibers one feels in placing the finger in the opening behind the symphysis are blood vessels, part of the Medusa like group of vessels that converge about the bladder as seen from above. If these vessels are torn and bleed it is almost impossible to stop the bleeding from below but when the space of Retzius is opened from above and the top of the bladder visualized it is easy to find the

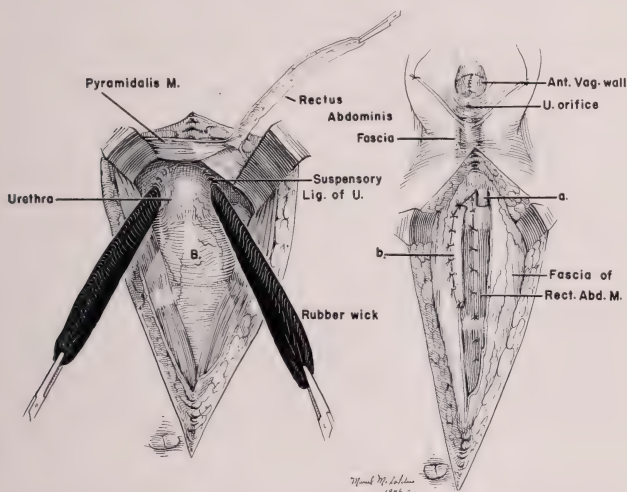


FIG. 3. The drawing on the left shows the space of Retzius opened. The fascia has been removed from above the right rectus muscle down to its attachment at the symphysis. The piece of Miller wicking placed on either side of the urethra from below has been recovered and is held tight to pull the broad urethra up into sight. The end of the rectus fascia is sutured to the end of the rubber wick and is pulled under the urethra and sutured alongside the rectus fascia on the left side of the wound. The fascial strip goes through the rectus muscle aponeurosis, then under the urethra, up again through the left rectus muscle aponeurosis, and is anchored by interrupted silk or cotton sutures along the edge of the cut fascia.

On the right is a faneul view of the rectus fascia going through the right rectus about the urethra which has been isolated through an incision in the anterior vaginal wall and up again and through the left rectus muscle insertion and is held by sutures along the cut edge of the fascia of the left rectus muscle. The fascia of the rectus muscle is later closed in the midline.

bleeding vessels and ligate them. After the vagina is closed the patient is then placed in Trendelenburg position and a midline incision is made with the incision going to the right of the umbilicus. The rectus fascia is isolated and incised and the pyramidalis muscles are recognized and dissected out. The incision in the fascia is carried down to the symphysis. Then a strip of fascia is elevated from the rectus muscles starting at the upper part of the incision and carried down to the symphysis and not detached. This strip should be about  $\frac{1}{2}$  inch wide. This

fascial strip can easily be torn across at the white line unless it is recognized that there is a weak area here. With a certain amount of care it can be lifted off and a long strip cut for the sling. The space of Retzius is opened by pulling the bladder away from the symphysis. The bladder neck and the urethra are easily recognized and the openings on either side of the urethra that were made from below are located by finding the piece of gauze or rubber left at the vaginal part of the operation. The fascial strip is then threaded through an opening in the rectus muscle tendon at the symphysis, sutured to the end of the gauze or rubber wick, and pulled under the urethra. It is then placed thru the opposite rectus muscle tendon at the symphysis. The fascial strip is then sutured to the fascia of the rectus muscle on the other side, thus anchoring it in place.

A real problem is to decide how much tension should be placed upon the sling. This is a matter of experience but I believe it should be firmly suspended. It will then be noted that the fascial strip is around the neck of the bladder and upper part of the urethra. The wound is then closed and the patient sent back to the ward. Constant drainage should be kept up for at least seven days; the catheter is then withdrawn and the patient allowed to void. It is often difficult for the patient to void so that it is necessary to keep the patient in the hospital longer than anticipated. Inability to void at first is a good sign. In the end, however, all patients have been able to void, although in one patient the act had to be done in the standing position. From the time of the operation to discharge there is no special care necessary, the only problem being the question of spontaneous voiding. The operation as described above is not difficult and it is easy to combine it with any abdominal operation that might be necessary, such as total hysterectomy, etc.

#### MATERIAL

In this series 19 cases were selected because of definite incontinence of the type that occurred during coughing, sneezing, or any stress. They were of all ages and parity. Many patients were cystoscoped first and urine cultures were done but all investigations were negative except for varying amounts of cystocele and weakness of the neck of the bladder. In nearly all cases previous operation had not been done. It was considered essential that the operation should be first done on primary cases.

The first patient was operated upon on February 9, 1943 and the last one in July, 1946. There were 15 patients whose operative results varied from fair to excellent and the four others were no better than before operation. In the first three cases no plastic of any type was done from below but in all the others a plastic, as described above was carried out. There were seven patients in whom total hysterectomy was done at the same time; five of these had excellent results; one, good; and one, fair. In 12 patients a plastic and a repair of the urethra plus sling was done. It is interesting that this group who had a total hysterectomy in addition gave the best results, due perhaps to a more perfect restoration of the normal anatomy of the bladder support. Of the 15 cases with a satisfactory result 10 were classed as excellent, there being no urinary difficulty of any



sort. In 3 the result was considered as good; one having frequency and nocturia and a slight incontinence when lifting heavy objects; another has urgency and if she does not answer her call to void quickly will leak slightly, but there is *no* stress incontinency. Another loses control not more than once a day. Two cases were classed as fair; one is slightly incontinent at night in bed but has no day time or stress incontinence, and the other occasionally wets her bed and has frequency but has no stress incontinence. Four were considered as poor results. In two the complaints are so vague and the patients so neurotic that it was impossible to do anything but classify them as failures for they do occasionally become incontinent. There is no consistency in their answers to questions and as a true end result cannot be determined they are called failures. One of the other two has severe diabetes; her fascial sling can be seen at cystoscopy holding up the trigone but there is bulging below. This, according to the theory of position and sagging, might account for the incontinence which is severe. She might have some sort of diabetic neuritis affecting the bladder but this cannot be proved. Dr. G. G. Smith, who has seen her in consultation, cannot suggest any way to close the area at the neck when, as he says, he can see no sphincter at all. She could not close the bladder outlet in any way voluntarily or involuntarily. The fourth failure was a patient who developed an abscess during her convalescence and drained the abscess out through the vagina. The operation was redone and failed again and later Dr. Fletcher H. Colby performed a Macky operation upon her and now, at the end of a year, she can sometimes go without a pad. She is a failure due perhaps to sepsis during the first attempt to cure her. Eleven patients have been followed for over a year, six for two or more years and two for over three years, and in these cases the results vary from good to excellent.

The results therefore can be considered as permanent. In a number of cases it took from two to seven months before the success or failure of the operation could be determined. This may be due to the length of time to regain muscle tone or to the tightening about the urethra that comes later with the formation of scar tissue. In six patients at follow-up it was stated that a crease could be seen on vaginal examination where the band crossed under the urethra. In one patient, the diabetic, it was considered that the patient was made worse by the operation. In no patient did any vesico vaginal or urethro vaginal fistula develop.

#### DISCUSSION

The cause of incontinence of urine in the so-called "stress" cases may be due to a disturbance of the proper anatomical support of the floor of the bladder and urethra rather than to intrinsic muscle or muscle nerve injury. Correction of the deformity gave good results in cases where no attempt was made to reconstruct the urogenital diaphragm. The sling operation, either of the Aldridge or of this type, can be recommended but its use should be limited to those patients in whom a plastic operation from below has failed. The results of the Kennedy and Kelly techniques are so satisfactory that an attempt should be made to cor-

reet the anatomical floor from below before resorting to fascial sling operations. The sling operation is not difficult and should entail no surgical risk. A difficult part of the operation is to decide how tight the fascial sling should be. Care must be taken to avoid surgery of this type in the very neurotic patient for evaluation of the amount of difficulty before and after operation is most difficult. The problem of the diabetic patient is a serious one and perhaps further study and investigation will show her failure as being due to her systemic disease rather than a problem in mechanics.

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## A CONTRIBUTION TO THE TECHNIQUE OF REMOVING LARGE CERVICAL FIBROMYOMAS

JAMES RAGLAN MILLER, M.D.

*(Hartford, Connecticut)*

The object of this communication is to describe a technique which the author has found useful in affording speedy and relatively bloodless mobilization in removing large cervical fibromyomas. Six abbreviated case histories are reported which, it is interesting to note, include all of the cervical fibromyomas measuring over 6 cm. in diameter which were diagnosed at the Hartford Hospital between 1935 and 1945.

In studying the records of cervical fibromyomas at the Hartford Hospital it was noted that several were incorrectly diagnosed since the fibroids originated in the fundus and had prolapsed through the cervix. No fibroid should be called cervical unless it originates in the cervix and develops below the endopelvic fascia. Not only is this a good dividing line from a theoretical point of view but practical as well. Large fibroids which develop above the endopelvic fascia are a much simpler problem for the surgeon.

If the operator is not wary and does not suspect the presence of a cervical fibroid he may cut into the bladder on entering the peritoneal cavity, for this viscus is often elevated almost to the level of the umbilicus. The operator is usually faced with difficulty of mobilization. There is no posterior pelvic fossa, and though it is easy enough for him to care for the round ligaments and tubes and ovaries, he is apt to get into difficulty and serious bleeding when he tries to push down the bladder, for this must be done often for a distance of 8 or 10 cm., and he is sure to encounter severe bleeding.

The technique which is here reported was first utilized in operating on E. K. (No. 508-096).

In this case it seemed evident that the cervical fibroid was held down by a stout fascial covering, and the operator reasoned that an incision of this capsule would permit enucleation of the tumor. The uterine vessels were easily identified, clamped and cut. By upward traction on the ends of the clamped uterine artery, the endopelvic fascia could be demonstrated covering the fibroid like a capsule. One blade of the large Mayo scissors was inserted under the fascia and it was found that the incision could be extended with great ease to the midline about  $1\frac{1}{2}$  cm. below the point where the fascia fuses with the utero-cervical junction. A similar incision was made on the other side and it was found that the fascial incisions could then be enlarged posteriorly on both sides as far as necessary. The whole fascial layer underneath the bladder could then be separated from the tumor, carrying with it all the bladder vessels with relatively little bleeding. It was a simple matter with a tenaculum, to deliver the cervical fibroid through the incision which had been made in its restraining fascial covering. The vagina was easily identified and incised and the rest of the operation was simple.

The surgeon who seldom performs a total hysterectomy does not become acquainted with the endopelvic fascia. Only when the cervix itself is removed is

he conscious of the fascial layers which are the real supporting elements of the urogenital hiatus. In the operation for total removal of the uterus, if the operator is careful to unite this fascial layer, there will seldom be a prolapse, and if union is not provided for, a prolapse may occur in spite of other accessory methods employed for its prevention.

The most significant aspect of the technique advocated is that it is possible to effect great mobilization of the bladder without disturbing the large bladder veins. The dissection is carried underneath the fascia instead of above it for the veins lie above the fascia and not underneath it. Just as a gynecologist can perform a relatively bloodless repair of a cystocele provided he keeps his dissection below the fascial plane, so in separating the bladder from a cervical fibroid, bleeding can be kept to a minimum by keeping within the proper planes.

In the writer's experience the ureter invariably has been pushed far outside of the field of operation whenever a true cervical fibroid has been encountered. The chances of injuring it are much less than when the fibroid is developed in the broad ligament above the endopelvic fascia.

Mention should be made also of the suggestion made by Curtis in his textbook, that the top of the vagina can be located by having an assistant pass a probe from below to the top of the vagina during the operation. This is helpful where the fibroid is developed in the posterior part of the cervix, but is of less assistance when the cervical fibroid lies in the anterior portion.

#### CASE REPORTS

*Case 1.* (#352-297) J. R., 51 years. Ward Service of J. R. M. Gravida 2, Para 2. Last previous period, February 1937. Two to three months before admission she noted vaginal bleeding, swelling of the left leg, pain and sense of heaviness in the left thigh. There had been a feeling of fullness in the lower mid-abdomen for the past year. No urinary symptoms were noted except occasional loss of control.

On pelvic examination the pelvic floor was well preserved, there was a copious bloody discharge, no cystocele or rectocele. The vagina was filled with what was taken to be a submucous fibroid about the size of one's fist, 10-12 cm. in diameter. Cervix appeared to be 6-7 cm. dilated and the physician who first examined her thought it would be possible to remove what he took to be a submucous fibroid by morcellation through the cervical opening.

*Operation.* (April 29, 1938.) After disinfecting the vagina with Lugol's solution, a large part of the prolapsed fibroid was morcellated with scissors with only moderate bleeding. It was found that no pedicle could be reached and that the implantation in the cervix was very broad. A 2 inch gauze pack was therefore placed in the vagina and a laparotomy was done through a lower midline incision. The uterus itself was found only slightly enlarged, the adnexa were atrophic, though there were large dilated veins, especially on the right in the ovarian ligaments. The fibroid was developed posteriorly so that the uterine arteries coursed forward and over the edges of the tumor, making it easy to clamp and ligate. No transfusion was necessary and an uninterrupted recovery took place. The tumor itself measured 9 cm. in diameter and was developed below the uterine arteries in the cervical canal. Another fibromyoma 4 cm. in diameter was found in the fundus.

*Case 2.* (#352-504) G. B., 32 years. Ward Service of J. R. M. Admitted May 1, 1938. Gravida 1, Para 1, 8 years previously. For the past six months her periods have been irregular, every two or three weeks interval, lasting ten days. She has noted a lump in her right side for six months. Two days before admission she felt a sharp pain in right lower quadrant accompanied by nausea. For several months there has been frequency of voiding and marked nocturia. Intercourse has been impossible because of pain for over a year.

Pelvic examination showed considerable muco-purulent discharge. The vagina was filled with a mass the size of a full term fetal head, moderately movable upward. The external os of the cervix from 3 to 9 o'clock was stretched out by a bulging, soft, fibroid-like tumor estimated at 9-10 cm. in diameter. The anterior cervical os from 9 to 3 o'clock was a narrow rim of tissue stretched over the above mentioned tumor. At the upper pole, anteriorly, there was felt a small mass which was thought to be the fundus. Hemoglobin was 49 per cent. One transfusion was given before operation, and two after the operation.

*Operation.* (May 3, 1938.) The vagina was cleansed with Lugol's solution. On opening the abdomen a small fundus was found on top of a cervical fibroid the size of a full term fetal head. The left tube and ovary were allowed to remain. Total hysterectomy was done removing the adherent right tube and ovary with great difficulty. Uterine arteries and veins ran very high up the sides of the tumor. Considerable bleeding was encountered and a moderate degree of shock from which the patient recovered without further difficulty. Mobilization was recognized as the principal difficulty in this operation. The actual tumor measured 15 cm. in diameter.

*Case 3.* (#354-550) A. D., 50 years. Ward Service of J. R. M. Gravida 5, Para 5. One previous admission, 9 years ago. Amputation of the cervix and perineorrhaphy. Increasingly scanty periods during the past 10 years. She had been examined every six to twelve months and slight erosion of the stump of the cervix was cauterized from time to time. One year previously, her physician, an experienced gynecologist, told her that she had a fibroid in the lower part of the uterus. This grew rapidly during the past year, and she was referred for operation. There were no other symptoms of note.

Examination showed a well sustained pelvic floor repair. The entire pelvis was occupied by a tumor which felt like a fibroid and which was estimated to be 11-12 cm. in diameter. It appeared to originate in the anterior fundal wall, very low on the cervix. The tumor could be seen bulging slightly through the canal of the repaired cervix.

*Operation.* (June 15, 1938.) Vagina was carefully cleansed with Lugol's solution. On opening the abdomen a normal sized fundus was found on top of a cervical fibroid estimated at 12 cm. in diameter which appeared to be developed below the level of the uterine arteries as much anteriorly as posteriorly. Mobilization was extremely difficult until the vagina was incised. Considerable bleeding was encountered deep in the pelvis from veins in the paravaginal tissue. She received one transfusion on the following day and made an uneventful recovery. The body of the fundus measured 6 cm. in diameter and the tumor actually measured 12 cm. Follow-up examination showed good recovery.

*Case 4.* (#481-751) A. G., 58 years. Private Service of J. R. M. Gravida 1, Para 1. The patient had last been well two years previously since which time there had been increasing frequency of voiding. This led to treatment by her local physician without benefit. Her last period was at the age of 55. She had always bled very severely, but aside from a curettage, and possibly a removal of a polyp many years ago there has been no local treatment, or examination during recent years.

Examination showed a huge fibroid-like tumor filling the entire pelvis and rising nearly to the umbilicus. The cervix was located anteriorly, high behind the symphysis. It seemed obvious that this was the cause of her urinary symptoms.

*Operation.* (March 29, 1944.) The vagina was carefully cleansed with Zephiran, though this was difficult because of the large bulging pelvic tumor. On opening the abdomen the appendix was noted to be atrophied and was not removed. The tumor was found to be a cervical fibroid and developed posteriorly entirely below the level of the internal os. Both tubes and ovaries showed the effects of an old chronic inflammatory process and were adherent. Removal of the right tube caused considerable difficulty. The adnexa were clamped at the uterus and dissected outward and finally ligated at the pelvic brim. Separation of the peritoneum from the anterior surface of the tumor mass led immediately into a large vein and the bladder itself could not be pushed down without producing more bleeding. Mobilization was extremely difficult but the cardinal vessels in the broad ligament on the right were severed, the vagina entered and after the top of the vagina was cut it was possible to remove the tumor going from right to left, as was suggested many years ago by Howard



A. Kelly. The patient made an uneventful recovery. No transfusions were necessary. An endometrial polyp was found in the uterus and a small pseudomucinous cystadenoma of the ovary was noted. The cervical fibroid itself measured 14 cm. in diameter.

*Case 5.* (#508-096) E. K., 58 years. Private Service of J. R. M. Gravida I, Para I. (A difficult delivery.) This patient was referred by her local physician because of an irritating vaginal discharge and a sense of pressure in the pelvis. Her blood pressure was found to be 220 systolic and 135 diastolic, and her physician said that it had been at this high level for a long time. Menopause was at 43, accompanied by considerable menorrhagia.

Examination showed considerable moisture and irritation about the vulva from the vaginal discharge which was purulent and which originated in the upper vagina. Diagnosis of a large cervical fibroid was made. A vaginal cavity communicated with a very deep pocket the end of which could not be reached with a probe as it ran very high on the right. Across the mass, protruding into the vagina, there was seen a vein  $\frac{1}{2}$  of an inch in diameter. Because of her high blood pressure and short thick set stature a difficult procedure was anticipated. Patient came into the hospital and rested 5 days before operation, during which time the vagina was irrigated and she was given 4 gms. of sulfadiazine daily.

*Operation.* (May 10, 1945.) Cleansing of the vagina was very inefficiently done because of the size of the tumor and the danger of injuring a large blood vessel. On opening the abdomen a small uterine fundus was found perched on top of a large cervical fibroid the size of a full term fetal head which carried the bladder upward and forward, covering half of the lower abdominal area. The ovarian veins on each side were very large. Numerous adhesions were separated between the sigmoid, tube and ovary. The round ligaments were first divided and the bladder was pushed down somewhat. The uterine arteries were identified coursing upward on each side in the dense capsule-like endopelvic fascia which seemed to surround and cover the cervical fibroid holding it down securely in the pelvis. The uterine vessels were clamped and cut and the fascial layer was then undermined with relative ease. The tumor was delivered after the peritoneum posteriorly was cut starting from the right uterine artery area and working across the pelvis. On cutting across the vagina, mobilization was easily accomplished. The rest of the operation was not difficult. Sulfanilamide crystals were sprinkled in the pelvic operative area. Continuous spinal anaesthesia was used, which was very satisfactory and no syncope occurred. Numerous granulomatous lymph glands were removed from the bifurcation of the iliac vessels. The cervical fibroid measured 15 cm. in diameter. Examination of the granulomatous lymph glands was highly suggestive of tuberculosis, which diagnosis would fall in line with the fact that she had for years attended a husband who had an open tuberculosis. The possibility of a Boeck's sarcoid was suggested.

*Case 6.* (#514-780) M. R., 53 years. Private Service of J. R. M. Gravida 0. She has been menstruating regularly with some intermenstrual spotting, though more heavily and longer during the last few months. She had lost 14 lbs. in weight and has had a heavy dragging sensation in the abdomen. This patient weighed only 97 lbs. when first seen.

On pelvic examination the cervix was found under the symphysis on the left, the true pelvis being occupied by a large fibroid tumor which reached two fingers below the umbilicus, filling also both lower quadrants.

*Operation.* (June 5, 1945.) After careful cleansing of the vagina with Zephiran the abdomen was opened and a fibroid tumor was found solidly filling the entire pelvis. The largest portion was developed under the peritoneal reflection in the broad ligament on the right side and on the left under the endopelvic fascia. The bladder was located high on the tumor. The round ligament on the right and the ovarian vessels were first ligated and cut. The ureter was immediately located and followed underneath the uterine artery which was doubly ligated and cut. It was clear that on the right side the fibroid was developed entirely above the endopelvic fascia although underneath the peritoneum and the upper folds of the broad ligament. The left round ligament was then ligated and cut. The

rectum and left adnexa were firmly adherent to the tumor, clamps were placed close to the tumor and cut and ligated. The uterine artery on the left side rode up on the cervical fibroid, was clamped and cut, and the dissection was carried inside the endopelvic fascia forward to the midline. The ureter on this side did not become visible at any time. When the tumor was brought up, as it was easy to do at this point, it was found that another soft fibroid was present in the cervix involving the posterior vaginal wall of the upper vagina. This was removed, cutting across the vaginal wall, and closing the vagina as usual. The rest of the operation was uneventful. The appendix was also removed. No transfusion was needed and the patient made a good recovery. The overall diameter of the specimen was 15 cm.

## VENOUS THROMBOSIS AND PULMONARY EMBOLIZATION IN OBSTETRICS AND GYNECOLOGY

HAROLD NEUHOF, M.D.

(*New York, N. Y.*)

There appears to be a rather generally held impression that venous thrombosis in the lower extremities and its complicating pulmonary embolism are more commonly encountered after parturition or gynecological operations than after non-pelvic procedures. Various causes for this assumed predilection have been invoked, such as the pressure of the enlarged uterus against the veins at the pelvic outlet, the position of flexion of the legs maintained for vaginal plastic operations, the fixation of the legs for operations performed in the Trendelenburg position, etc. There are also those who visualize venous thrombosis occurring within pelvic veins to be the result of stasis from pressure of tumors or of trauma to blood vessels during operation.

In a study of venous thrombosis which was made at Mount Sinai Hospital over a number of years I have seen in consultation virtually all patients with venous thrombosis (with or without the complication of pulmonary embolization) on the Gynecological Service of Dr. I. C. Rubin. Although I have not kept a score I think it safe to say that according to my experience the incidence of venous thrombosis after gynecological operations was not appreciably greater (if at all greater) than after general surgical operations. A greater proportion of cases from the Gynecological Service have come to operation for venous thrombosis, with or without complicating pulmonary embolization, than on some of the general surgical services. The reason may lie in a greater awareness of the desirability of treating such cases by operation rather than expectantly, on that gynecological service. Accordingly, it is not only as a tribute to Dr. I. C. Rubin but also as a pleasure because of the progressive stand he has taken in the management of the problem of venous thrombosis that I present a viewpoint on the subject reached from a study of venous thrombosis carried on over a number of years.

From the foregoing it may be said that the problem of venous thrombosis and pulmonary embolization is not different after gynecological than after general surgical operations. Although more or less general agreement on this statement can be hoped for there will be no ready acceptance of the thesis that the problem is the same in obstetrics. Here long standing traditions and teachings must be overcome, and that is not easy particularly when decisive evidence is not forthcoming. Nevertheless, the logic is clear. Venous thrombosis developing in a leg during pregnancy or after parturition presents the same features as venous thrombosis after operations or unrelated to operations for that matter. Perhaps the added factor of the pelvic state may be properly invoked to account for the extreme lesion termed *phlegmasia alba dolens* (which one might prefer to term

venous thrombosis with extreme lymphatic blockade). By and large however the etiology of the venous thrombosis is the same as in other conditions, and, of vital therapeutic importance, one must assume that the mechanism of pulmonary embolization is the same. Only when there is a general appreciation of this fact will there be any planning to obviate the horrible tragedy of fatal pulmonary embolism after childbirth. At the moment there appears to be a widely-held view that early rising from bed after childbirth is a solution to the problem of venous thrombosis and pulmonary embolism just as many believe this to be true after general surgical operations. Unfortunately the problem is not to be solved so simply and all one may logically anticipate after early rising from bed is a reduced incidence of venous thrombosis. The argument would become unnecessarily complicated if one entered at length into a discussion of venous thrombosis in ambulant patients or the occurrence of pulmonary embolization, fatal at times, so soon after operation (or parturition) that extensive venous thrombosis must have existed in the lower extremity before operation (or childbirth). It can be hoped that obstetricians will debate this subject at their meetings and ponder the problem as some in the fellow specialty of gynecology have done.

The problem of venous thrombosis which, it is maintained, is virtually the same in obstetrics as in gynecology can be discussed under 1. Etiology, 2. Symptoms and signs, 3. Prophylaxis, 4. Treatment by drugs, 5. Treatment by operation. I shall not attempt to touch on many of the controversial features of the subject disseminated through an enormous literature but shall confine myself largely to some personal observations made during a study of the subject.

1. Concerning the etiology of venous thrombosis it may be said that there is only one common denominator upon which there is general agreement, namely the slowing of the circulation in the deep veins of the feet and legs which may occur (or occurs regularly) when adults lie in bed even for a period of a few days. Thus the source of pulmonary embolization in virtually all cases is a propagating thrombus in the femoral vein which has extended upwards from the deep calf veins. The pelvic or other veins cannot be invoked as sources (regardless of whether or not they are also the seat of thrombosis) either on the law of probability or on that of mechanism. In order to produce massive pulmonary embolism at any rate, the fragment or fragments lodged in the pulmonary artery or its branches must be derived from a substantial thrombus (femoral or iliac vein) in a more or less straight line with the inferior vena cava. The etiology of pulmonary embolization therefore is venous thrombosis in the deep veins of the lower extremities usually extensive enough to have propagated upwards to the femoral or even iliac veins. Once this fact is realized the importance of recognizing not only venous thrombosis in the legs but also the existence of minor grades of pulmonary embolization is realized. Some features of the diagnosis of the latter will be discussed in the next paragraph but it should be stated at once that, as in the case of venous thrombosis, the diagnosis of minor pulmonary embolization may be difficult or even impossible. The study which we have

made of major pulmonary embolization<sup>1</sup> reveals how often the lungs may be showered with silent pulmonary emboli. The phenomenon termed infarction which may be regarded as a more or less accidental hemorrhagic infiltration complicating embolization appears to be essential if symptoms of peripheral pulmonary embolization are to appear.

2. The symptoms and signs of venous thrombosis range from the obvious to none. However, it should not be assumed that the more evident the symptoms the greater the likelihood of the existence of thrombophlebitis rather than venous thrombosis. I have repeatedly found the femoral veins to be the seat of a thrombosis of identically soft consistency and the vein as free from reactive inflammation in cases characterized by obvious symptoms as in those essentially or entirely symptom-free. Furthermore, the assumption that the existence of thrombophlebitis with its obvious signs and symptoms (not venous thrombosis or so-called phlebothrombosis) precludes the possibility of pulmonary embolization even of the fatal variety, is false. The text-book symptoms and signs of venous thrombosis will not be discussed, but it can be said that they are present perhaps more often than is generally assumed, if carefully sought for. It should be more widely known however that fever and rapid heart action persisting more than a few days after operation or parturition may properly be ascribed to venous thrombosis in the lower extremities if search elsewhere for their cause has been unrevealing. A recent illustration is that of a patient who pursued a febrile course for 10 days after hysterectomy without any evidence of infection in the chest or in the operative field. The gynecologist in charge was fully aware of the possibility of venous thrombosis as the cause and had examined the legs repeatedly for signs of that condition. Because measurement of the circumference of the calves and thighs revealed comparative increase on the left side venous thrombosis on that side was diagnosed despite absence of other signs. At operation there was found a propagating thrombus in the left femoral vein which extended to within a short distance of the inguinal ligament. This increase in the circumference of one calf or in both with bilateral involvement is a good sign of venous thrombosis and those who are interested in attempting to discover, at a relatively early stage, the existence of venous thrombosis would do well to take basic measurements of all patients at the beginning of bed stay and check up on changes in circumference at frequent intervals. Formal attention will be called to this procedure in a future publication, but I wish to make passing reference to it here.<sup>2</sup> An additional diagnostic feature to which attention will also be called is the presence of infiltration in the calves, often attended by tenderness. This sign has been found in the presence as well as in the absence of the classic Homan's sign.

Another illustration which is particularly revealing because of the type of

<sup>1</sup> H. Neuhoef and S. Klein: Massive Pulmonary Embolization, A Study of 88 Fatal Cases. Appearing serially in the Journal of the Mount Sinai Hospital. To be published as a Mount Sinai Hospital Monograph.

<sup>2</sup> Paper by H. Neuhoef and A. Sarason, to be published.



febrile course is that of a young woman in the sixth month of pregnancy who had fever of a septic type after having been confined to bed for several days on account of a grippal infection. When seen after more than a week of oscillating fever the significant feature of the examination was infiltration and tenderness in one calf. Fever subsided promptly after ligation of the femoral vein and infiltration in the calf soon subsided.

The importance of venous thrombosis is of course its relationship to pulmonary embolization. A conservative view would be that venous thrombosis requires therapeutic consideration only if pulmonary embolization has occurred. Even on the assumption of such a view serious thought should be given to the recognition of the existence of pulmonary embolization. I have said that the course of the latter may be a quite silent one, but that is rare. The rapidly fatal variety is known to all but it is perhaps not so generally known that the diagnosis of death due to coronary occlusion or to other cardiac lesions is not infrequently made in such cases. The fatal episode is not uncommonly preceded by episodes which may also be non-characteristic. When, in addition, there may be no symptoms referable to the legs and when, if in fact, not much may be found in an examination of the legs when venous thrombosis is specifically sought for, the occasional difficulty of the problem of diagnosis becomes apparent. A tragic recent experience will serve as an illustration. A woman of 35 was discharged from the hospital 12 days after a simple abdominal operation. The convalescence was uneventful yet the surgeon made almost daily examinations of the calves for the possibility of venous thrombosis. The examinations were negative. One week after leaving the hospital the patient went to the doctor's office for a check up. She stated that, the day before, she felt weak and faint going to the bath room, but recovered in about an hour. Examination at the office revealed slight infiltration but no tenderness in one calf. The patient went home because hospital admission could not be had, and went to bed. 36 hours later there was a sudden episode of collapse soon terminating fatally. The autopsy revealed an occluding embolus in the pulmonary artery.

Post-operative pneumonia is not infrequently diagnosed in cases of infarction because the typical triad of infarction—localized thoracic pain, hemoptysis, afebrile state—is probably seen in less than half the cases. A discussion of the differential features, including the roentgenographic, would lead too far afield. One may say however that post-operative pneumonia, when it occurs, is a suppurative bronchopneumonia in virtually all cases and therefore to be recognizable as such. In other cases the pulmonary lesion may be in the nature of atelectasis complicating suppurative bronchitis and bronchiolitis. Hence pulmonary embolism rather than pneumonia may be assumed to exist if the aforementioned lesions, usually not difficult of diagnosis, can be excluded.

It is the milder, transient, manifestations which must be identified as pulmonary embolization and thus as warnings of more serious episodes which may supervene. Even the slightest and most transient localized area of thoracic pain, with minimal or no physical signs, should lead to a film of the chest which

may reveal the shadow of an infarct of even substantial proportions. This disclosure followed promptly by ligation of one or both femoral veins (in accordance with the presence or absence of signs of thrombosis in one or both veins) may be life-saving. The more carefully fatal cases of pulmonary embolization are studied the more frequently it appears that the fatal episode was not the first intimation of the existence of that lesion or of a preexisting venous thrombosis. Undoubtedly the rapidly fatal pulmonary embolism which "comes out of a clear sky" does occur but is not common in carefully documented cases.

3. The prophylaxis for venous thrombosis in the sense of prevention has been one of the most widely discussed subjects in medicine in the past decade. There is very little to offer at this time because of such great conflict of views and of the necessary lack of supportive evidence for many of the views which are maintained. It is not even known if there is a predilection for the development of venous thrombosis amongst certain physical types although for example the stout and overweight and those with "sluggish circulation" in the lower extremities are singled out by some. Others are of the opinion that a predisposition to thrombosis can be invoked in many cases. The one fact which is proven is the common occurrence of the lesion. A crucial study was made by Neuman in 1938. He examined the veins by serial section in 165 consecutive autopsies on adults who died of a variety of diseases. Venous thrombosis in the legs which propagated upwards to various levels was encountered in 100 cases. Of parallel significance was the incidence of peripheral pulmonary embolization in 34 per cent of his cases and massive (central) pulmonary embolization in 12 per cent.

Neuman's work is conclusive and final insofar as it concerns patients who lie in bed for varying periods of time and ultimately die of their disease (or occasionally of pulmonary embolism complicating venous thrombosis in the legs). In patients who often suffer from minor illnesses and who are not necessarily confined to bed the demonstration of venous blockade by venography was the outstanding contribution of Bauer. Although his method cannot be depended upon always to establish the existence of venous thrombosis it was fundamental for it proved first, the great frequency of venous thrombosis in the legs even when least suspected, secondly the tendency towards rapid extension upwards of the thrombotic process, and thirdly the likelihood of detachment of the upper end of the thrombus because of its lack of attachment to the wall of the vein. Of particular interest here is the fact that Bauer is a gynecologist (practicing in Mariestad in Norway) and that the cases studied and treated by him were largely obstetric or gynecological patients.

It is evident that Bauer's work tends to minimize the assumed factor of slowed circulation in the legs from more or less prolonged bed stay as the cause of venous thrombosis. The assumption which as I have said is the one common denominator, namely that of slowed circulation from bed rest, becomes weakened still further when attention is called to a small but important group of cases of venous thrombosis developing in ambulant patients, that is patients who have not remained in bed because of any illness or indisposition. To discuss this

group here would lead too far afield and it is only mentioned in connection with the question of prophylaxis.

The numerous recommendations which have been made for the prevention of venous thrombosis are scarcely worthy of mention because so many which have been advocated appear to have been replaced by other recommendations often by the same author. The truth of the matter appears to be that there is as yet no method of preventing the development of venous thrombosis except by the use of anticoagulants. On the other hand there appears to be considerable logic in the assumption that certain measures may *reduce* the incidence of venous thrombosis or perhaps more accurately stated (because the incidence is presumably so high) to limit its widespread propagation. Here belong such measures as regularly performed leg exercises, the avoidance of tight binders, frequent and whenever possible early rising from bed after gynecological operations or after delivery. The views concerning the avoidance of constriction around the knees in gynecological operations are too well known to be repeated but it might be said in passing that one well-known authority was of the opinion that firm bandaging of the legs after operation prevented the occurrence of venous thrombosis and thus solved the problem of pulmonary embolization.

From the foregoing as well as from much evidence to which reference has not been made the conclusion to be drawn is that venous thrombosis can be prevented only by the administration of anticoagulants. Here one is faced by difficulties and vicissitudes accompanying the intravenous administration of heparin (which is ideal anticoagulant) and, on the other hand, the delay in action, the necessity for frequent laboratory determinations, and the limited margin of safety in the case of dicoumerol. Only when an anticoagulant can be safely, painlessly, and simply administered as in the case of penicillin, for example, can the widespread administration of an anticoagulant be practiced and only then will the problem of prophylaxis of venous thrombosis as well as that of pulmonary embolism be approached on a large scale. Such a method of administration will be reported upon in the near future.<sup>3</sup> If its further trial on a large scale substantiates the present impressions which are held, there will be available a method of universal applicability of anticoagulation therapy.

4. The treatment of venous thrombosis which has been recognized as existing in one or both lower extremities can be considered from the viewpoint of drug therapy, operative therapy, or a combination of both. In this discussion I shall venture to present the viewpoint I now hold rather than attempt to offer a summary of views which are so greatly at odds at the present time. It is only fair to state that there are those who believe that the "conservative" treatment of venous thrombosis, by which they mean no treatment, suffices. According to this group, which is by no means small, the chances for pulmonary embolization are so remote that, statistically, one may on the whole do more harm than good by "meddlesome" surgical or even anticoagulant therapy. Whether there are

<sup>3</sup> By D. Stats and H. Neuhof, Am. J. M. Sc. (in print).

proportionately more general surgeons than gynecologists who hold this view I do not know but I think it safe to say that all will more or less gradually assume a different viewpoint as the tragedies of the *laissez faire* management are brought home to them. As I have said there is at the moment the hope or even the belief amongst many that the problem is solved by getting the patient out of bed almost as soon as the operation has been terminated but this will not be at best more than a partial solution of the problem, one may be sure.

Concerning the treatment of existing venous thrombosis by anticoagulants it can be said that not only theoretically but also actually, according to reports in the literature, there is the danger of detachment of the upper portion of the thrombus and resultant pulmonary embolization. There also is the danger of bleeding into the operative field in the administration of anticoagulants shortly after a gynecological operation. In obstetrics there may be a number of inponderables in anticoagulation therapy after parturition. Accordingly, the truly conservative viewpoint today would appear to be the consideration of operative rather than anticoagulant therapy for venous thrombosis, reserving anticoagulant therapy for cases in which surgery would appear to be undesirable for one reason or another. At the same time I may express my conviction that the theoretical objections are only theoretical and that the time will come when the management of venous thrombosis by anticoagulant therapy will be regarded as standard and safe. It is likely that this view will be reached when large numbers of uniformly successful cases treated by safe anticoagulant therapy are reported in the literature.

Again, referring to the present time, the safest treatment of venous thrombosis should be regarded as operative, if an episode of pulmonary embolization has occurred. The operative treatment of venous thrombosis with or without pulmonary embolization now will be discussed.

5. The operative treatment of venous thrombosis in the absence of pulmonary embolization usually is simple because thrombosis generally extends as high as the level of the femoral vein only when pulmonary embolization occurs. Thus the operative treatment generally consists of simple severance of the common femoral vein under local anesthesia. Although the recommendation of ligation of the superficial femoral vein has been made by some the procedure does not obviate the possibility of the escape into the circulation of an embolus, even of a fatal one, from a thrombus in the profunda femoris vein, and should therefore not be considered since the basic purpose in ligation of the femoral vein is not to cure venous thrombosis but to prevent a fatal pulmonary embolus. The severance of the common femoral vein should be carried out between ligatures because of the possibility of encountering a thrombus at the level of the section always exists.

The question of bilateral ligation in the presence of known venous thrombosis in one leg has not been settled. In the absence of pulmonary embolization it is my opinion that ligation should be limited to the limb in which there is clinical evidence of venous thrombosis. Where pulmonary embolization has

occurred bilateral ligation is indicated unless the thrombus has extended on one side to or above the femoral vein (under which circumstances this side can be assumed to be the source of the embolus) or unless there is clinical evidence of thrombosis which has extended to the level of the femoral vein on both sides (under which circumstances both veins should be operated upon because the source of the embolus may have been from either side). There have been a few instances in my experience in which one side has been operated upon to be followed days or weeks later by operation on the other side as clinical evidence of upward extension of the thrombotic process on that side appeared (with or without renewed embolization).

The operative management of thrombosis which has extended up into the femoral or iliac veins or beyond has not been standardized. Some cut into the vein in all cases to determine if there is free bleeding, extracting a thrombus through the incision if a thrombus is present. Others ligate or attempt to ligate above the assumed upper level of the thrombus, even if a ligature on the vena cava is required. After a trial with various methods a number of years ago I have employed the following technique in a considerable number of cases with results which have been so satisfactory that more radical methods do not appear to be warranted. Recovery of the patient in virtually all cases (unless the episode of pulmonary embolization has been severe) and but little morbidity from operation can be anticipated.

The important point to remember is that the thrombus within the vein may be so soft and the change in the appearance of the vein so insignificant if in fact any change exists that the presence of a thrombus may not be suspected before the vein is incised. The common femoral vein is therefore dissected free with extreme care and no handling. Two ligatures are placed well apart and the vein is severed between ligatures. The presence of a thrombus at the level of section is established indubitably. The administration of heparin is begun in order to obviate the likelihood of recurrence of thrombosis after the removal of the clot. The ligature on the upper end of the vein is removed, fine clips applied to the cut end, and an attempt to remove the thrombus by suction is begun. In cases of extension of thrombosis into the external iliac vein and beyond, instrumental removal of the thrombus is often required. The extent of upward extension of the thrombus may be much greater than anticipated, even into the vena cava. In any event removal of thrombotic masses should not be discontinued until truly free bleeding has occurred. The vein is then securely ligated, transfixion sutures being employed to obviate later hemorrhage from the stump.

In my opinion the operative treatment of venous thrombosis is urgent because the time of occurrence of pulmonary embolization, fatal or otherwise, can never be gauged. It is doubly urgent if pulmonary embolization, be it ever so mild, has occurred, for the next episode which may be the fatal one may occur within a short time of the warning one. It is important to remember that a mild clinical episode of pulmonary embolization can be due to a large



thrombus lodged in a large branch of the pulmonary artery and that therefore to minimize an episode of pulmonary embolization because it is mild or an infarct because it is small may be tantamount to signing a death warrant.

How shall the advantages of the surgical treatment of venous thrombosis with or without pulmonary embolization which are obvious be balanced against the disadvantages? The latter consist in the possibility that the operation may have been unnecessary, the patient's condition may not have been good at the time of operation, or the local effect of operation may have been untoward. The last mentioned feature warrants some consideration. The untoward effects are edema of the leg and, rarely, the development of an ulcer of the varicose variety. Edema is not common and persists in only a small proportion of the cases. Persistent edema to a pronounced extent is almost as rare as ulcer. Under both circumstances the evidence points to the likelihood that the extensive venous thrombosis would have produced the persistent edema or ulcer if operation had not been performed. When, following hundreds of ligations, little or no edema is the rule it may be regarded as logical to assume that the ligation of the vein in itself played little or no rôle in the evolution of the untoward result. This logic is fortified by the fact that, as reported by me in various places at various times, ligation of the main venous trunk of an extremity, upper or lower, is not a competent producing cause of edema. Edema is due to lymphatic and not to venous blockade. It is therefore fair to conclude that the advantages to the gynecological or obstetric patient of the surgical treatment of venous thrombosis without embolization or with embolization far outweigh the possible disadvantages of operation, the uncertainties of nonoperative therapy, or the dangers of so-called conservative treatment.

## ADENOACANTHOMA OF OVARY ARISING FROM ENDOMETRIAL CYST, WITH REPORT OF A CASE

EMIL NOVAK, M.D.

(*Baltimore, Maryland*)

*From the Department of Gynecology, Johns Hopkins Medical School*

We know very little about the histogenesis of most of the many types of ovarian carcinoma. There is very little doubt that the surface epithelium of the ovary is the source of a good many of these growths, including quite surely the serous papillary cystadenocarcinomas and the more solid forms of papillary carcinoma. Again, there is good evidence as to the dysontogenic origin of granulosa cell carcinoma, arrhenoblastoma and dysgerminoma, although modifications of the prevailing explanations may be called for in future years. This group, however, is a comparatively small one. Perhaps the largest group of primary ovarian carcinomas is made up of the adenocarcinomas, and we can only speculate as to their origin, although there has always been a tendency to ascribe this to the so-called germinal epithelium of the ovary, a tissue of notoriously great differentiating potency.

The establishment by Sampson (1) (1921) of pelvic endometriosis as a definite and very frequent pathological entity rather naturally raised the question of whether or not the ectopic endometrium so often occurring in the ovary could not be the seat of adenocarcinoma, just as the latter so often occurs in the endometrium of the uterus itself. It was Sampson himself who first raised this question in 1925. In this publication he very justifiably urged that since ectopic endometrium exhibits the same biological reactions as does that of the uterus, there is no reason why it could not be the seat of adenocarcinoma, like the uterine mucosa itself. The biological similarity of ectopic endometrium to that of the uterus is shown by the fact that marked secretory and even strikingly progestational changes may be seen in ovarian endometrium, although frequently the ectopic endometrium is of immature type, and may show no evidence of such secretory change even though the uterine mucosa reveals typical progestational changes. In the same way, ovarian endometrium may or may not undergo decidual transformation in pregnancy. Hyperplasia of typical Swiss-cheese pattern is a not uncommon finding in areas of ovarian endometrium, while atypical hyperplasia of pseudomalignant appearance has likewise been noted, as pictured, for example, in Fig. 32 of Sampson's paper.

The pattern of at least some adenocarcinomas of the ovary is strikingly like that of adenocarcinoma of the uterus, but this in itself has little significance, especially since both the endometrium and the germinal epithelium have a common coelomic ancestry. Nor can the coexistence of endometriosis and carcinoma be considered to indicate an origin of the latter from the former, though it would be considered at least suggestive. If, however, an adenocarcinoma can

be demonstrated as springing from the lining of an endometrial cyst, few would doubt the significance of such a picture.

Of the group of cases studied by Sampson some are strongly suggestive of the possible origin of adenocarcinoma in endometrial cysts, a few highly probable, and one, especially his Case 5, entirely convincing. It is surprising that, since the publication of Sampson's paper, so few observations have been made on this point by others, in spite of the great frequency of both endometriosis and ovarian carcinoma. The attitude of most pathologists appears to have been to concede the theoretical possibility of such malignant transformation in endometrial cysts, but to attach little importance to it in the histogenesis of ovarian carcinoma in general. This is quite possibly the correct viewpoint, as thus far so few indisputable instances of such a relationship have been reported.

That carcinomatous changes can occur in the ectopic endometrium of adenomyosis has apparently been shown in a small group of reported cases, and similar malignant changes have been described in endometrial areas on the posterior surface of the uterus, as in the cases reported by Vogt (2) and Reinhardt (3). A number of authors, like Seitz (4), too, have also emphasized that pelvic endometriosis has an influence in exciting cancer growth in neighboring organs, especially the bowel, but the evidence on this point is not convincing, especially in view of possible errors in microscopic interpretation.

It is doubtful that the study of full-blown or advanced adenocarcinoma of the ovary can yield any information as to its possible endometrial origin. In smaller growths, especially those showing any chocolate-colored content, there is a better prospect of securing information on a possible relation of endometriosis to adenocarcinoma. Even more productive would be the study of endometrial cysts showing papillary ingrowths into the cavity. Such cysts, however, are exceedingly rare, to judge from the extreme paucity of reported observations. While a number of authors like Taylor (5) and Stevens (6) emphasize ovarian endometrium as a source of adenocarcinoma which must be considered, they report no cases of this group. In none of Taylor's large group of 121 cases of malignant ovarian tumors, for example, was such a histogenesis invoked. Nor do there appear to be any other undoubted cases in the literature.

I have recently had the opportunity of studying a case of adenocarcinoma arising in the wall of an endometrial cyst, the only one I have personally observed in which such an origin seems to me beyond any question. This material was sent to me by Dr. P. W. Butterfield, pathologist of the Washington County Hospital in Hagerstown, Md., to whom, as well as to Dr. H. R. Kritzer, who operated on this patient, I am indebted for permission to report the case, and for supplying me with a few clinical data.

#### CASE REPORT

The patient, Mrs. C. H. K., was a married white woman of 32, whose previous health had been good. She had been married for a number of years, with no pregnancies. Menstruation had been entirely normal, with rather short intervals of about 3 weeks. Her only complaint was of lower abdominal pain. She had had a pelvic examination 4 months before admission to the hospital on March 31, 1946, and at that time a pelvic tumor, thought to be uterine, was discovered. Pregnancy tests had been negative.

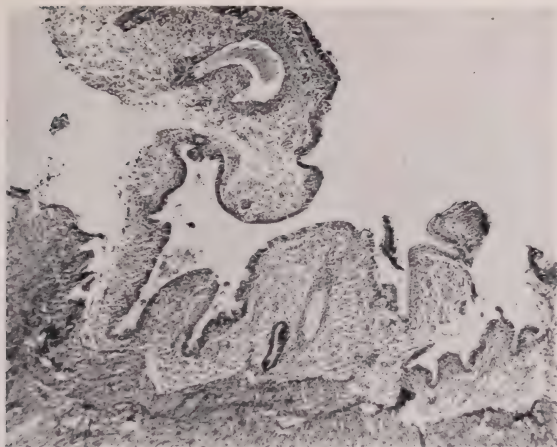


FIG. 1. Showing the lining of the endometrial cyst proper

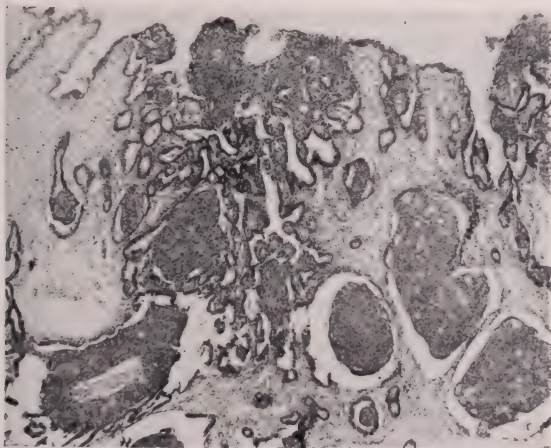


FIG. 2. To show the line of demarcation between normal endometrium and the malignant growth

At operation on April 2 a large chocolate cyst of the ovary was revealed, together with a small cyst of similar character in the left ovary, and a bilateral hydrosalpinx. The operation consisted of right salpingo-oophorectomy, left salpingectomy, resection of the small cyst of the left ovary, and appendectomy. The postoperative course was uneventful.

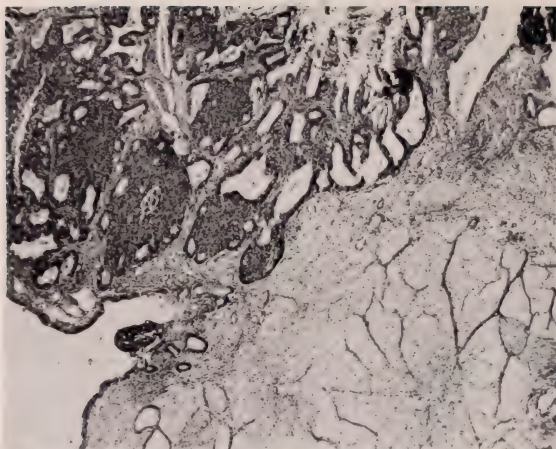


FIG. 3. Typical adenoacanthoma, similar to adenoacanthoma often seen in endometrium of uterus. Note the strip of normal endometrium at left

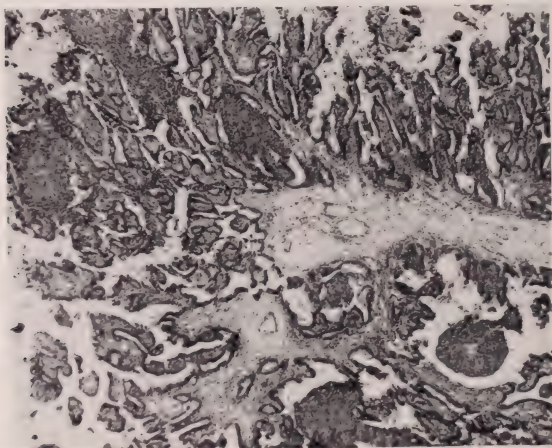


FIG. 4. Section from friable polypoid tumor arising from wall of endometrial cyst

Dr. Butterfield reports that the right ovarian mass measured 10 x 6 x 3 cm. A cystic cavity measuring 5 cm. in diameter, filled with dark brownish fluid presented at one point a friable papillary mass, about 2 x 1.5 x 1 cm. Adjoining this was a second small cystic



cavity communicating with that described above. The small endometrial cyst in the other ovary unfortunately did not reach the laboratory. Sections and later blocks of the right sided tumor were sent to me for examination.

The microscopic examination leaves no doubt as to the existence of a typical endometrial cyst, as shown in Figure 1. In direct continuity with the endometrium, from which it obviously springs, is the papillary mass above described, and Figure 2 shows the line of demarcation between the endometrium and the growth. Figures 3 and 4 show more characteristically the appearance of the papillary growth, revealing it to be a typical adenoacanthoma. The glands are moderately atypical with stratification and de-differentiation of the epithelial lining of many of them. Especially interesting are the numerous large plaques of squamous cells adjoining many of the glands, and apparently budding into some of them. Some of the larger plaques show central degeneration, but there is no suggestion of any anaplastic activity in these squamous areas.

The fact that the malignancy arising in this endometrial cyst assumed the form of adenoacanthoma seems to me to be highly significant, and to point all the more strongly to the endometrial origin of this growth. Such acanthomatous changes are practically never observed in the ordinary types of ovarian adenocarcinoma, while on the other hand adenoacanthoma is a relatively frequent form of endometrial carcinoma as observed in the uterus itself.

#### SUMMARY

A case is reported in which, in a patient of 32, an adenocacanthoma arose from the wall of an endometrial cyst. Since the extensive acanthomatous changes associated with the adenocarcinoma in this patient are not observed with the ordinary adenocarcinomas of the ovary, and since they are not uncommon with endometrial carcinoma, the evidence for the endometrial origin of the malignancy in this case seems all the more complete. This case, and at least one of Sampson's, appear to be the only ones in the literature in which the possibility of such an occurrence is clearly established, in spite of the frequency with which both ovarian endometriosis and ovarian adenocarcinoma are encountered clinically. There is no justification therefore for considering that an endometrial origin can be invoked in the explanation of any large number of ovarian carcinomas.

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*Addendum.* Since this manuscript was submitted two additional reports on this subject have been published. Gunnar Teilmann (*Act. Obst. et Gynec. Scandinav.*, 25: 377, 1945) describes one case of this type, and Kuzma (*Am. J. Obst. & Gynec.*, 53: 245, 1947) reports two instances, one unquestionable and one, at least, highly probable.

# QUANTITATIVE AND QUALITATIVE CHANGES OF THE SERUM PROTEINS IN NORMAL AND TOXEMIC PREGNANCY. THE NATURE OF THE HYPOPROTEINEMIA IN PREGNANCY

JOSEF NOVAK, M.D. AND BERNARD LUSTIG, Ph.D.

(New York, N. Y.).

*From the Chemical Laboratory and Obstetric Service of Beth Israel Hospital and the Research Laboratories of Lawrence Richard Bruce, Inc. Work done under the A. Krasne Research Fund*

Various authors (1) state that the protein concentration of the blood is lowered in pregnancy, and assume that an excess in this dilution of the blood plasma leads to latent and manifest edema and finally to eclampsia. Recent publications (2) compare this hypoproteinemia in pregnancy with other types of hypoproteinemia due to insufficient protein intake or uncompensated protein loss. According to these authors, the pregnancy hypoproteinemia is caused by an inadequate intake of protein, and can be prevented and cured by a protein-rich diet.

The favorable results obtained by a high protein diet in the prevention and treatment of toxemias in pregnancy are apparent and shall not be denied. However, this therapeutic success does not necessarily prove that the regular "physiologic" hypoproteinemia in pregnancy is the result of a protein-poor diet, nor that the latter is the primary and basic cause of the late pregnancy toxemia. Such an assumption is in contradiction both to the findings of some older (3) and of some more recent (4) investigators, who found that in man as well as in experimental animals, pregnancy normally terminates with a gain in nitrogen which markedly exceeds the requirements of the fetus and its adnexa. Of significance also is the fact that eclampsia disappeared almost completely in Central Europe in the time of starvation and of widespread "famine edema" during and after the First World War, and gradually reappeared with the return to normal nutritional conditions. It is also an old, well-established fact that eclampsia is predominantly a disease of overfed women, and that in such cases a highly restricted and particularly a salt-free diet yields results as good as the newly recommended protein-rich one.

Only investigations which consider not only the percentage of the total protein in the blood, but also determine the total blood and plasma volumes can give a true indication of the real protein content of the blood. Since examinations of the blood and plasma volumes in pregnancy are scarce (5) and were disregarded by the authors who trace the hypoproteinemia to malnutrition, additional determinations of the relative and absolute protein content of the blood in pregnancy seemed desirable.

It is further known that there is not only a decrease of the total protein concentration in the blood in pregnancy, but also a marked shift in the albumin-globulin ratio. While the percentage of albumin is markedly decreased, the globulin and particularly the fibrinogen content is considerably increased. The decrease in the albumin-globulin ratio is particularly steep in toxemic pregnancy

(6). It seemed to be of interest not only to corroborate these statements, but also to attempt to determine possible changes in the composition of the blood proteins. Recent investigations (7) have shown that the bound carbohydrate content of the isolated serum proteins can be used as an indicator of changes in their composition under normal and pathological conditions. It seems possible that the normal as well as the pathological pregnancy may cause evident changes in the carbohydrate content of the various protein fractions of the blood serum.

In consequence of these considerations, the concentration of the total protein, the albumin and the globulin, and also the blood plasma volume and carbohydrate content of the serum proteins were determined in 22 normal and 7 toxemic pregnant women. Five of these women were examined during pregnancy as well as one to seven days after the delivery. In addition, the sera of 8 normal non-pregnant individuals were examined in the same way.

#### METHOD

The albumin and globulin content of the plasma were determined according to Howe, and the blood and plasma volumes by the method of Rowntree (8), using Congo red as indicator.

The carbohydrate and nitrogen content of the total serum protein and of the albumin fraction were determined after isolation from the serum. The difference between these two values gives the carbohydrate and nitrogen content of the globulin fraction. The protein content of each fraction was obtained by multiplying its nitrogen content by the factor 6.25. The carbohydrate values were expressed in per cent carbohydrate per 100 g. protein.

It was necessary to modify the orcinol-sulfuric acid reaction as used by various investigators (7,9) and for the carbohydrate determination. Different sugars and serum proteins gave the same brown color with the reaction. The colors follow Beer's Law. Readings of the color obtained with galactose, mannose, glucose and serum proteins were made between 400 and 700  $m\mu$  at intervals of 10  $m\mu$ , in the Cenco-Shear Spectrophotometer and gave absorption curves of the same shape but the relative amounts of absorption obtained with equimolar solutions of different sugars varied slightly. For the standard, a mixture of equal parts of galactose and mannose, similar in composition to the carbohydrate group determined in serum proteins at 520  $m\mu$  [see Rimington (7)], was used.

Further experience with the reaction showed that even protein alone, heated with 60 per cent by volume (v/v) sulfuric acid for 20 minutes at 80°C. without addition of the orcinol reagent, gave a yellow color, the intensity of which depended on the protein concentration. However, no color appeared when the orcinol reagent (2 per cent orcinol in 25 per cent (v/v) sulfuric acid) or sugar solutions alone were heated with 60 per cent (v/v) sulfuric acid under the same conditions. The absorption curve of the color obtained with protein and sulfuric acid was similar in shape to the sugar-orcinol absorption curve between 460 and 650  $m\mu$  with maximum absorption at 500 to 520  $m\mu$ . With 10-50 mg. of serum proteins it followed Beer's Law. The carbohydrate values of serum proteins were 3-5 per cent higher if sulfuric acid-orcinol reagent was used as a control instead of sulfuric acid-protein mixture. The method was modified to eliminate this error.

For the determination of the nitrogen and carbohydrate content of the total serum proteins, 5 aliquots of .1 ml. serum were diluted with .4 ml. water and the protein precipitated either by addition of 2-3 ml. alcohol or 2-3 ml. 5 per cent trichloroacetic acid. After 50 minutes' standing, the protein was centrifuged, 3-4 ml. alcohol added to the precipitate, and the mixture was heated for 3-4 minutes in a steam bath. After centrifuging again, the alcohol was drained off. This treatment removes all reducing sugars and most of the salts and lipoids from the protein.

TABLE I

NO.	AGE	MONTH OF PREGNANCY	BLOOD VOL- UME IN ML.		PLASMA VOL- UME IN ML.		SERUM PROTEIN		SERUM		A/G	CARBOHYDRATE CONTENT OF THE SERUM PROTEINS		
			Total	Per kg.	Total	Per kg.	in per cent	Total in g.	Alb. in g.	Glob. in g.		Total	Alb.	Glob.
A. Normal non-pregnant														
1	49		5242	63	3100	37	7.19	223	140	83	1.70	1.81	0.71	3.60
2	31		4725	79	2833	48	7.39	209	139	70	2.00	1.71	0.67	3.85
3	33		5200	67	3125	41	6.63	207	134	73	1.83	1.99	1.19	3.46
4	58		4320	66	2680	41	7.38	198	130	68	1.90	1.82	0.85	3.60
5	35		4729	93	2535	51	7.53	191				1.73		
6	35		4000	75	2452	47	6.25	153	100	53	1.97	2.05	0.93	4.14
7	27		4800	85	3001	53	6.92	208	148	60	2.49	2.17	0.83	5.55
8	32		4345	79	2550	46	7.04	179	120	59	2.02	1.50	1.07	4.41
Average.....			4670	76	2784	45.5	7.04	196	130	66.6	1.99	1.85	0.89	4.09
B. Normal pregnant														
1*	25	3	6346	92	3731	54	5.72	213	122	91	1.34			
2*	20	6	4848	95	2923	58	5.68	165	99	66	1.00	2.25	1.72	3.04
3	40	6	6032	90	3758	56	6.29	244	155	84	1.90	1.86	1.54	2.31
4	38	6	6253	95	3818	58	6.52	249	135	114	1.18	1.95	1.74	2.09
5*	22	6½	6208	96	3687	57	5.65	208	115	93	1.72	1.59	1.19	3.38
6*	21	6½	6897	86	3724	46	6.39	138	133	105	1.27	2.74	2.23	2.36
7	30	7	5481	93	3234	52	6.02	195	100	95	1.05	2.19	1.91	2.36
8	27	7	5771	99	3456	60	5.69	197	110	87	1.16	1.57	0.87	2.10
9	31	7	6074	70	3250	37	6.79	221	111	110	1.00	1.89	1.71	2.72
10	23	7½	6547	95	3909	57	6.23	241	139	102	1.32	1.46	1.10	1.94
11		7½	7160	94	4384	57	6.96	306	199	107	1.87	2.24	1.24	4.10
12	29	7½	7372	96	4305	56	6.50	280	166	114	1.47	1.83	1.37	2.56
13	25	7½	6447	92	3675	53	5.81	214	129	85	1.51	2.21	1.29	3.55
14	27	8	5527	85	3171	57	6.24	198	120	78	1.53	2.12	1.88	2.47
15	29	8	6621	92	3906	54	6.41	250	149	101	1.47	1.86	1.54	2.31
16*	28	8½	5105	81	2899	46	6.09	177	93	84	1.11	2.23	2.12	2.36
17	21	8½	5146	73	3000	43	6.10	183	116	67	1.73	1.95	1.74	2.32
18	35	8½	7278	95	4120	54	6.27	258	154	104	1.49	2.11	1.55	2.98
19*	21	9	7359	106	4141	60	6.72	278	159	119	1.33	2.02	1.52	2.71
20	38	9	5014	81	2922	47	7.08	207	106	101	1.05	1.74	1.60	1.88
21		9½	6740	74	3909	43	6.86	269	164	105	1.56	1.71	1.08	2.69
22	31	?	5000	84	2750	46	6.05	166	86	80	1.07	1.78	1.05	2.56
Average.....			6147	89	3576	52	6.28	225	130	95	1.37	1.96	1.54	2.61
C. During and after pregnancy														
1	23	7½ mon. 1 da. aft.	6547 5760	95 3000	3909 3000	57	6.23 6.17	241 185	139 96	102 89	1.32 1.08	1.46 2.43	1.10 1.31	1.94 3.65
2	29	7½ mon. 4 da. aft.	7372 4584	96 2613	4305 2613	56	6.50 5.19	280 135	166 68	114 67	1.47 1.00	1.83 2.75	1.37 1.80	2.50 3.71
3	31	7 mon. 7 da. aft.	6074 4359	70 2515	3250 2515	37	6.79 5.96	221 150	111 74	110 76	1.00 1.00	1.89 2.71	1.71 1.76	2.72 3.68
4	27	7 mon. 2 da. aft.	5771 4726	99 2924	3456 2924	60	5.69 6.10	197 180	110 99	87 81	1.26 1.25	1.57 2.62	0.87 1.39	2.10 4.11
5	40	6 mon. 5 da. aft.	6032 4160	90 2429	3758 2429	56	6.29 6.76	244 165	155 94	89 71	1.90 1.33	2.05 2.84	1.26 1.24	3.55 4.95

TABLE I (concluded)

NO.	AGE	MONTH OF PREGNANCY	BLOOD VOLUME IN ML.		PLASMA VOLUME IN ML.		SERUM PROTEIN		SERUM		A/G	CARBOHYDRATE CONTENT OF THE SERUM PROTEINS		
			Total	Per kg.	Total	Per kg.	in per cent	Total in g.	Alb. in g.	Glob. in g.		Total	Alb.	Glob.
D. Toxaemias														
1	44	4½ mon.	6005	98	3381	53	6.52	222	111	111	1.00	2.20	1.35	3.03
2	37	7½ mon.	6329	75	3500	42	6.66	233	115	118	1.08	2.53	1.78	3.57
3	31	7½ mon.	6944	81	4125	48	6.17	254	132	122	1.12	2.36	1.19	3.58
4	39	7½ mon.	4613	71	2786	43	7.21	201	100	101	1.00	2.15	1.25	3.05
5	38	7½ mon.	4839		3000		5.60	133	39	94	0.67	2.82	2.79	2.84
6	25	9½ mon.	6486		3950		7.11	281	135	146	0.93	1.86	1.50	2.22
* 15		?	4885		3273		6.34	206	89	117	0.61	2.29	1.36	3.04
Average.....			5729	81	3431	46	6.52	219	103	116	0.91	2.32	1.60	3.05

\* Primipara.

The alcohol should be checked for its neutrality. Alkaline alcohol gives slightly opaque solutions with corresponding loss of protein. The addition of a few drops of acetic acid to 1000 ml. alcohol will eliminate this behavior. Each precipitate was dissolved in .4 ml. of 1 per cent sodium hydroxide. The nitrogen content of two samples was determined after digestion with sulfuric acid (micro-Kjeldahl). The other three samples were used for the carbohydrate determination.

For the isolation of the serum albumin fraction, 1 ml. serum was precipitated with 15 ml. of 23 per cent sodium sulphate in the presence of ethylether, as suggested by Kingsley (10), and centrifuged. To each of 5 aliquots of 2 ml. of the filtrate in centrifuge tubes, 6 ml. of water were added. The tubes were heated for 5 minutes in a steam bath, then 2 ml. of 20 per cent trichloroacetic acid were added. After 15 minutes, the albumin precipitate was centrifuged, washed with 5 ml. 1 per cent trichloroacetic acid, centrifuged and re-dissolved in .4 ml. sodium hydroxide. Two samples were used for the nitrogen, and three for the carbohydrate determination.

For the carbohydrate determination in the isolated protein, two samples were mixed with .2 ml. of the orcinol reagent and 6 ml. 60 per cent (v/v) sulfuric acid, and then heated for 20 minutes at  $80^{\circ} \pm .25^{\circ}\text{C}$ . For the control, one sample of each determination was mixed with .2 ml. water and 6 ml. of 60 per cent (v/v) sulfuric acid and treated in the same way. After cooling with water to room-temperature, the color developed and was measured at 520 mμ in a Cenco-Shear Spectrophotometer. The values were expressed in terms of per cent carbohydrate present in the protein.

The results are summarized in Table I.

We wish to express our sincere thanks and appreciation to Dr. Ella Fishberg, chief of the Chemical laboratory of Beth Israel Hospital for much valuable advice and assistance.

## RESULTS

In agreement with the statements of other investigators, the figures of our table show that the concentration of the plasma protein is decreased in normal as well as in toxemic pregnancy. But on the other hand, they prove that due to the increased plasma volume, the total protein content of the circulatory blood is usually higher than it is in non-pregnant individuals. The average amount of the total serum protein is 225 gm. in pregnant, and 196 gm. in normal non-



pregnant women. Thus the hypoproteinemia in pregnancy means only a dilution of the plasma, and not a real lack of protein.

In toxemic patients there was no evidence of a further increase of the blood and plasma volumes, nor of a further decrease of the total protein content. An increased shift of water from the blood into the tissues and intensive spasms in vast vascular areas, both characteristic attributes of toxemia, apparently camouflage a probable exaggeration of the changes in the plasma volume and the plasma proteins.

Our figures show a significant decrease of the albumin-globulin ratio, which is particularly marked in toxemias. In the toxemic group, there are even three cases in which the amounts of globulin exceed those of the albumin. The average total albumin is 130 gm. in both non-pregnant and normal pregnant women. But considering the increase in blood plasma, this means a decrease in concentration from 4.66 per cent to 3.63 per cent. In the toxemic group, the average albumin concentration drops to 3 per cent. On the other hand, the average percentage of globulin is slightly higher in normal pregnancy than in the non-pregnant state (2.65 per cent as compared to 2.39 per cent) and is still higher in toxemic patients (3.38 per cent). Thus the hypoproteinemia in pregnancy follows the general rule that any decrease in the serum protein is mainly due to a decrease in the albumin fraction, which represents the main factor responsible for the regulation of the osmotic pressure of the blood plasma.

The investigations of women in the pregnant state and a few days after delivery are too scant to justify definite conclusions. They show a remarkable reduction of both the blood and plasma volumes. In spite of that fact, the hypoproteinemia was still present on the seventh day after delivery. The average total protein content of the circulatory blood in these cases was 236 Gm. in pregnancy, and 163 Gm. after delivery. Whether this decrease in total protein is due solely to a loss of blood at delivery and by the lochia, or whether it is also caused by a shift of protein from the blood into special depots, cannot be decided by our data.

Our assumption that there may be some changes in the bound carbohydrate content of the blood proteins in pregnancy proved to be correct. Though the carbohydrate content was approximately the same in the pregnant as well as in the non-pregnant state (averages 1.96 per cent and 1.85 per cent respectively), definite changes were found in the separate protein fractions. The carbohydrate content of the albumin fraction was increased in pregnancy (average 1.54 per cent as against 0.89 per cent in the non-pregnant state), while it was decreased in the globulin fraction (average 2.61 per cent against 4.09 per cent in non-pregnant women). In toxemic patients, the bound carbohydrate content was higher than in normal pregnant women both in the total protein and in the globulin fraction.

#### DISCUSSION

The regular occurrence of the hypoproteinemia in pregnancy in various countries with different nutritional conditions, the increased total protein content of the circulating blood, and the fact that pregnancy usually terminates with a net

gain in proteins, prove that the hypoproteinemia of pregnancy cannot be identified with a hypoproteinemia due to malnutrition. Moreover, if it keeps within certain limits, the hypoproteinemia of pregnancy is a physiological condition—an adaptation of the physico-chemical condition of the maternal blood to that of the fetus, whose tissues are far richer in water than those of the adult. In accordance with this, various investigations (12) revealed a low protein content of the fetal blood, and a striking approximation of the maternal albumin content to that of the fetus. The globulin content however, which does not influence the osmotic pressure essentially, was always greater in the maternal blood. According to all investigations, the same holds true to a still higher degree for the coarsely molecular fibrinogen. On the other hand, there is a higher content of amino-acids and some crystalloids in the fetal blood, which compensates for the higher amount of albumin in the maternal blood and keeps the osmotic pressure of both bloods at about the same level (13). To bear out this fact, several authors (14) found the same freezing point in both the maternal and the fetal blood.

The adaptation of the maternal and fetal osmotic pressures seems to be essential for the preservation of the vital nutritive chorionic epithelium of the fetal villi, which, in the human hemochorial placenta, dip directly into the maternal blood, and would shrink if they merged into a medium with higher osmotic pressure.

The tendency of the pregnant organism to retain salt and water, and to dilute the blood as well as the tissue fluids, is apparently the cause of the hypoproteinemia in pregnancy. Under normal conditions, it is not due to an insufficient protein intake. The tendency toward salt and water retention is probably caused partly by an increased function of the adrenal cortex which is in general markedly enlarged in pregnancy, and partly by the large amounts of estrogen and progesterone produced in the maternal organism.

In the years of famine in Central Europe after the first World War, the diet of pregnant women consisted mainly of carbohydrates and was poor in proteins, still poorer in fats, and also salt, thus preventing an excess of water retention and the outbreak of eclampsia. The undeniably favorable effect of a protein-rich but salt-poor diet can easily be explained by its antagonistic influence on an excessive salt and water retention. It is a similar but more expedient measure than the hypertonic glucose infusion, usually applied in eclamptic and pre-eclamptic women.

Our investigation of the bound carbohydrate content of the plasma proteins reveal some changes in the composition of the separate protein fractions. However, the biological and clinical meaning of these findings cannot be evaluated until we have sufficient experience concerning the carbohydrate content of the plasma proteins under various physiological and pathological conditions.

#### SUMMARY

1. The increase of plasma volume in pregnancy over-compensates the decreased protein concentration of the blood and results in an increase of its total protein content.

2. The hypoproteinemia due to a protein-deficient diet is therefore not identical with the hypoproteinemia of pregnancy. If this keeps within normal limits, it is a physiologic condition and indicates an adaptation of the maternal organism to the requirements and physico-chemical conditions of the fetus.

3. The carbohydrate content of the total serum proteins is roughly the same in pregnancy as in the nonpregnant state; the carbohydrate content of the albumin fraction is increased in pregnancy, but decreased in the globulin fraction. In toxemic women, the carbohydrate contents of the total serum proteins and of the globulin fraction are higher than in normal pregnant women. These differences indicate qualitative changes in the composition of the proteins in normal as well as in toxemic pregnancy.

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# A NOTE ON THE EFFECT OF A VITAMIN K-LIKE QUINONE UPON EXPERIMENTAL RENAL HYPERTENSION IN DOGS

B. S. OPPENHEIMER, M.D. AND LEONA ZACHARIAS, Ph.D.

(New York, N. Y.)

The therapeutic value in essential hypertension of any of the vitamins so far tested has not been established (5), with the possible exception of vitamin K. Other work as well as our own has shown an antipressor effect of the well-known quinone, vitamin K (menadione) on the high blood pressure of hyper-

TABLE I  
*Effect of 15 Daily Intramuscular Injections of Synkayvite on Hypertensive Dogs*

DOG #	DURATION OF HYPERTENSION BEFORE TREATMENT	AVERAGE OF SYSTOLIC BLOOD PRESSURE BEFORE TREATMENT*	DAILY DOSE OF SYNKAYVITE†	PERIOD TESTED	AVERAGE OF SYSTOLIC BLOOD PRESSURE DURING TREATMENT‡	FALL IN SYSTOLIC BLOOD PRESSURE
	months	mm. Hg.	mg.		mm. Hg.	mm. Hg.
250	13	201	10-38	15	193	8
256	12	188	10-38	15	180	8
257	12	192	10-38	15	189	3
261	3½	190	10-38	15	183	7
263	5	191	10-38	15	186	5

\* Each blood pressure given is the average of 5 control readings preceding treatment.

† During the 15 days of treatment with *Synkayvite*, the dosage was:

10 mg. for the first 2 days

20 mg. for the next 6 days

38 mg. for the next 7 days

total = 406 mg.

‡ Each figure is the average of 15 systolic blood pressure readings taken during the experiment.

tensive rats (1). Schwarz and Ziegler (2) demonstrated an antipressor effect in hypertensive rats with menadione, but failed to show any antipressor effect with the water soluble compound, 2-methyl-1,4 naphthohydroquinone, diphosphoric acid ester tetrasodium salt (*synkayvite*). They were considering trying vitamin K in human hypertension, but it has not been possible to learn whether or not they carried out any such experiments. Recently, however, Rosenthal and Shapiro (3) did observe a significant antipressor effect in about 50 per cent of human beings with essential hypertension following the administration of *synkayvite* either orally or parenterally.

Still more recently Moss and Wakerlin (4, 6) have found no significant effect on the blood pressure of six hypertensive dogs which received either vitamin K in sesame oil (menadione) or vitamin K powder (kappaxin). These six dogs received the compounds either orally, or in one case intramuscularly for periods of 3-6 months.

Quite independently, we investigated the effect of the water soluble vitamin



K, *synkayvite*, on five dogs rendered hypertensive by the application of the Goldblatt clamp to the renal arteries. No significant effect in reducing the high blood pressure of these dogs could be observed during or after the administration of this water-soluble vitamin K (table I). The dosage employed on dogs was as follows: 10 mg. for the first 2 days, 20 mg. for the next 6 days, 38 mg. for the next 7 days, making a total of 406 mg., injected intramuscularly, in 15 days.

#### DISCUSSION

Our findings on dogs do not necessarily conflict with those of Rosenthal and Shapiro on human hypertension, as the identity of essential hypertension in man and the hypertension of Goldblatt dogs is still in doubt. It may well be that *synkayvite* is effective in human hypertension in spite of the failure to demonstrate any antipressor effect of either the water soluble or the fat soluble vitamin K in hypertensive dogs. It has been established that vitamin K (menadione) reduces the high blood pressure of experimental hypertension in rats, but not in dogs. It is obvious that in the field of hypertension one cannot directly transfer the results of experiments from one species of animal to another. Moreover, it should again be noted that non-specific agents administered parenterally have been known to produce depressor effects in hypertensive humans and in experimental animals.

#### SUMMARY

The administration of a vitamin K-like quinone in large doses to hypertensive dogs has not resulted in any significant reduction of blood pressure.

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## AN OLD PHOTOGRAPH

REUBEN OTTENBERG, M.D.

(*New York, N. Y.*)

When I received the suggestion to contribute to the I. C. Rubin Anniversary, I remembered an old photograph which had been lying in my desk many years. It was made in Berlin in 1910. And the center of the group of six American students, all fresh from Mount Sinai was the freshest of them all, I. C. Rubin (fig. 1).

The photograph brought back to my mind innumerable memories; it came from an interesting phase of medical education,—a phase which is dead and will never return. I thought that nothing would be more appropriate than to write a few recollections of that year in Berlin and the men who were there with me. These, I hope, will interest not only the men of my own generation, many of whom lived through the same experiences, but the younger men, who never will.

The six men shown in the photograph were only a few of the great number of American physicians then studying in Europe. In those days American medical education was not what it is now. The revolution resulting from the great work of Abraham Flexner and the A. M. A. classification of medical schools as Class A, B, C, or D, had not yet taken place. Many of our medical schools were still staffed chiefly by practitioners who did a few hours of teaching a week. If the graduates of the better schools were for the most part excellent physicians, it was rather because they were earnest students and good material to start with, than because of the quality of the teaching. Post graduate teaching in America was in the horse-and-buggy stage. If a man wished technical training in any specialty he generally went abroad. It will be noted that each of the men in our photograph studied abroad what he subsequently made as his life work.

American and other foreign students seldom registered at the University. They took private courses in technical subjects like cystoscopy (Hyman and Rubin) or bronchoscopy (the late Louis Kaempfer) both then brand new specialties,—or they attended clinics and lectures. Later, after learning the language, many of them became volunteer assistants or did what was called an "Arbeit", i.e. directed research. In either case they paid fees directly to the professor who depended on these for an important part of his income. This was one of the grave defects of the European system. It led to a commercial type of competition among the teachers and to exploitation of the patients. It was well known that in certain cities or hospitals students could even do major surgery on the patients if they paid the professor well.

I. C. Rubin's work in Berlin was supplementary to his study of gynecological pathology already completed in Vienna under Professor Schottlander, who had taken great personal interest in him. In Berlin he studied pathology with Ludwig Pick at the Friedrichshain Hospital, but especially at the Landau Gynecological Clinic on Philipstrasse. He took morphology and did experimental work on the omentum of cats and dogs which he subsequently published.

I also worked with Ludwig Pick who, though a great pathologist, was only an "ausserordentlicher Professor". The title "ausserordentlicher Professor" was really only an honorary one, something like "Clinical Professor" at a university-affiliated institution here; it was not a real university appointment. Pick was a striking personality, a man of vast knowledge and considerable originality, looking anything but the scholar that he was. In fact he gave the impression of a typical bachelor about town; he was barely five feet high, jolly and excessively fat, and (when not in the laboratory) he dressed in a manner that might have been called foppish. He treated me very kindly—in fact left me in



FIG. 1.

Reuben Ottenberg  
Murray H. Bass

Edgar D. Oppenheimer  
Isadore C. Rubin

Abraham Hyman  
Morris Munker

charge of the post-mortem work at Friedrichshain during his summer vacation. (Incidentally I got the good meals intended for him and served in his private office). Under his tutelage I wrote an article on Froelich's syndrome (published in German), and though he did most of the work he insisted on its publication under my name. In spite of his admirable qualities I never warmed up to him or received much stimulation from him. It was probably my own fault for Eli Moschcowitz, who had been there a couple of years earlier, had received great inspiration.

In 1914 Rubin went back to Schottlander in Vienna with the idea of taking supplementary work in gynecological pathology. Schottlander put him through a stiff examination and told him to go home; there was not much more he could teach him to make it worth while to stay. That was fortunate for him because immediately afterward the first world war broke out.

Murray Bass' principal study was in pediatrics with Finkelstein who was then introducing some revolutionary ideas in infant feeding; he also worked in pathology with Benda, the local rival of Pick.

Abe Hyman, like Rubin, had already completed much of his European study in Vienna. In fact Hyman and Rubin were companions nearly all their stay abroad. They both took cystoscopy courses and worked at Bumm's famous venereal clinic at the Charite (the "Bellevue" of Berlin). Post graduate students were allowed to practice cystoscopy on the clinic patients, so that in a couple of months they had more experience than the "resident" in an American hospital sometimes attains in as many years.

Jerry Leopold (then recently graduated from Mount Sinai) was also in the group though not in the photograph. Like Bass he studied pediatrics with Finkelstein. On returning he was appointed to the staff at Lenox Hill Hospital where he subsequently became attending pediatrician and moved entirely out of the Mount Sinai orbit. However, he kept up his intimacy with I. C. Rubin with whom he has maintained the habit of dining once a week for all these years.

Beside pathology with Pick my own study consisted of serology (especially the, then new, Wassermann Reaction which I learned from Wassermann's assistant, Meyer),—and chemistry which I took with Peter Rona at Friedrichshain. Rona was as different from Pick as a man could be: glum, tall, cadaverous looking, black bearded, he reminded one of a mediaeval talmudic scholar. He tried hard to make a chemist of me, but my almost complete innocence of elementary chemistry made it difficult. Like Pick he had me publish a German article under his sponsorship, embodying an original idea of his for the formol titration of nitrogen.

Vienna was a better organized center for study than Berlin, but in Berlin there were half a dozen brilliant stars who attracted the Americans. Most of the men in our photograph studied in Vienna also, I thought of doing so. But when I visited Vienna and spent an afternoon with Karl Landsteiner, (with whom I intended to work), he struck me as so eccentric and nervous, that I was scared off, and never even mentioned to him that I had applied his observations on isoagglutination in an actual transfusion in 1908 and had published a footnote pointing out that the blood groups were inherited according to the Mendelian law. That afternoon Landsteiner was so intent on demonstrating his then new discovery of the transmissibility of poliomyelitis that blood groups were not even mentioned. In subsequent years, when Landsteiner came to the Rockefeller Institute, I got to know him, and to recognize his eccentricities as those of an authentic genius.

Beside the special work of each we all wandered about making occasional visits to the public clinics of the various great men.

Murray Bass has a vivid recollection of the meeting at which Paul Ehrlich presented the results of the treatment of his earliest cases treated with "606." There were, for example, several cases of congenital syphilis in which mouldages had been prepared of the whole infant showing the lesions, and looking absolutely lifelike. These models, made before treatment, were shown together with the

living, cured infant. When Ehrlich stood up on the platform to speak before the packed hall, he was greeted with a roar of applause such as one sometimes hears at the recital of a famous musician. Everyone rose. He was so overcome, that tears ran down his cheeks.

Freidrich Kraus was the most popular of the internists. His clinic started promptly at 8 a.m. and there was standing room only. If you did not get there early, you did not get in. His brutality to his patients was only matched by his clinical brilliance and wide knowledge.

The inconsiderate way in which charity patients were treated left a permanent impression on me. Compared with it the treatment of patients in our American city hospitals was and is extremely humane. The hospitals were equipped for the scientific study of the patients rather than for their comfort and cure; and they were treated very much like so many guinea pigs. The hideous human medical experimentation of the Nazis was not an accident but was the natural flowering of something that had been growing in Germany for many years.

Murray Bass recalls an incident. It was in the clinic of Professor Joseph, one of the most celebrated dermatologists of his time. A shivering woman was standing on a chair, clad only in a profuse pustular eruption, and surrounded by a crowd of forty doctor-students, from all the corners of the world. "Let's see if the colleague from America can make a diagnosis" said Joseph as he turned to Bass. "Scabies" said Murray. "No" said Joseph, as he asked another man with his sarcastic tone: "what does the colleague from Russia think?"—"Small-pox perhaps" came the answer. The crowd edged away. "False," said Joseph. "Scabissimum"—ultra scabies. Bass heaved a sigh of relief.

There was another peculiarity of German professors (or indeed of Germans in general), illustrated by the following authentic incident. I met a certain really famous professor (whom I will not name: he was a Baron to boot). As we stood talking in the street he pulled from his pocket a long cigar; then, to my surprise, took a short scissors and cut the cigar in half. I thought that he, (perhaps having only one cigar), was about to offer me half of it. However, he lit one half, put the other half safely back in his vest pocket and continued the conversation.

The Mount Sinai men dwelt in two chief centers in Berlin, the first a rather luxurious "Pension" or boarding house on Karlstrasse, run by a prim Hungarian lady, Mme. Jendritza. It was a large establishment which fed as well as lodged its guest, had facilities for recreation and provided considerable social life. All except myself in our photograph lived there at the time, as did several other Mount Sinai men, notably Walter Highman, subsequently dermatologist to the Hospital.

Mme. Jendritza herself was the chief "source of innocent merriment." She was very insistent on the propriety of her establishment and warned each newcomer carefully. She would ask her guests pointedly "Where were you last night, Dr. So and So." Moreover she saw that her rules were enforced; and used to sit at the door at night until the last student was in to make sure that the monastic sanctity of her institution was not violated.



She regarded Americans as somewhat insane on the subject of baths, tooth-brushes and ice water. Once an American woman-student from Portland trying to brush her teeth, and confused by the complicated array of knobs and handles in the bath room, turned the wrong faucet and got the shower bath full on her head. "Serves her right" said Mme. Jendritza, "it will teach her not to brush her teeth so often."

Edgar Oppenheimer (who subsequently was associate orthopedist at Mount Sinai, and in 1934 became attending orthopedist at Beth Israel Hospital) had, and retained until his death this year (1946) a keen sense of humor and a liking for practical jokes. He amused himself by writing occasional amorous postal cards (signed with various girls names) to himself and the other men at the *pension*. Everyone but Mme. Jendritza was in the secret. She (never failing to read anything that came within her reach), would go into a fit of indignation at such goings on, to the intense delight of everyone else.

Rubin and Hyman consorted with a crowd of artists and musicians. Hyman and Bass were pretty good violinists. One evening they organized a musicale at Mme. Jendritza's. The old lady was anxious to do something really big for her Americans. She knew how they loved ice; so as a refreshment she served a big bowl of chopped ice of which everyone present solemnly partook so as not to embarrass their hostess.

I. C. Rubin today is a mild and gentle soul, but, on one occasion in Berlin, his temper matched the then color of his hair (nearly auburn—though on the house staff he was known as "White Rubin" to distinguish him from Mark S. Reuben who was known as "Black Reuben"). It happened when Rubin, Walter Highman, his charming wife Heloise, a young lady guest of theirs and I were at a cafe and an army officer swanked by and swung his heavy sheathed sword so that it cracked the young lady's shins. He walked on without even attempting to apologize. In a flash Rubin confronted him. The manager of the place had to separate and soothe the two so as to avoid an "international incident."

All the six faces on my old photograph are familiar to subsequent generations of Mount Sinai men except the one seated at the right, Morris Munker. He was an extraordinary fellow—probably the most brilliant young clinician of his generation. While a junior interne he recognized the first case of *spina bifida occulta* ever diagnosed in America, (subsequently written up by one of his attendings, Walter Brickner). He had already at that time the diabetes, which caused his death only a couple of years later. Insulin was still over ten years in the offing, and although he knew very well the invariable course of diabetes at his age, he kept on studying like a demon.

The second students' center in Berlin to which I referred above was in Philipstrasse 6. It was a much more modest affair than Jendritza's and was inhabited by men whose pocketbooks were more limited than their ambitions. It was kept by a Frau Nikolaus, the anemic looking, blond wife of a German working man: they had, as I remember, two rooms to rent to students in their walk up apartment, which was on the fourth floor.

The most interesting of their domestic arrangements was the bath. The

taking of a bath (charged for as an extra) was so elaborate a ceremony that if anyone had asked for it more than the standard once a week, I am sure our Hausfrau would have collapsed. The water had to be heated by burning briquets of compressed coal or coke in a huge porcelain stove. A big sheet was spread in the tub and over its sides so that the bather would not slip.

During my first six months I shared a room there with Albert A. Epstein (subsequently associate attending physician at Mount Sinai and now attending at the Joint Disease and Beth Israel Hospitals). He was working at the "Charite" with the famous Professor Salkowski and with Magnus Levy, the "discoverer of basal metabolism." Eugene F. Dubois (afterward professor of medicine at Cornell) was working there the same year. I used to wonder at the huge complicated respiration chambers and other apparatus with which they played. It was Dubois more than anyone else who subsequently simplified the whole procedure of metabolism rate testing and established it as a clinical method in America. Epstein was already dreaming (very, very secretly) of the application of Starling's physiological principles of osmotic equilibrium to human disease. I did not understand at the time why he was so much concerned over the concentrations of proteins in serum and transudates. His classical papers on edema and blood proteins (after his return home) opened up whole new fields of clinical thought.

Professor Magnus Levy is still alive, a refugee in New York. Last year the late Dr. Libman gave an 80th birthday party for him and Dubois made the principal speech.

Epstein used to have to report to the police court every fortnight. He had sailed from New York in a hurry and had neglected to provide himself with a passport. After long delay and endless investigation he finally got one.

During the second half of my year in Berlin my room-mate in Philipstrasse 6 was Abraham L. Garbat who had been a fellow interne with me at the Lenox Hill (then German) Hospital, where he subsequently was attending physician. I had graduated there but had moved over and become pioneer Fellow in Pathology, at Mount Sinai (as holder of the then brand new George Blumenthal Jr. Fellowship). Garbat had wealthy relatives in Berlin and got about socially quite a bit. With him I became acquainted with a charming American couple, Louis and Anna Gruen, who were extremely kind to us. Garbat went in especially for serology, bacteriology and gastro-enterology,—a peculiar combination that helped him greatly when in the First World War he was in charge of an army hospital for infectious diseases and made the original studies on typhoid carriers subsequently published as a Monograph of the Rockefeller Institute. That work was so thorough that practically nothing of importance has been added to the subject since.

Frau Nikolau served us coffee and a roll for breakfast, we used to take a hot midday meal at a restaurant and to bring home delicatessen and rolls and pastry from the little bakeshop downstairs in our own building; thus we prepared our own supper.

My favorite restaurants were what the Germans called "gut buergerlich." The fare was plain but hearty: for a few cents you had your fill of sausage,

sauerkraut and beer. In my romantic head I somehow thought I was "going native." Actually I made very few personal contacts with the citizens. There was one beerhall that I particularly liked, the "Pschorrbrau." It was much frequented by the student "Corps" (fraternities) with their distinctive caps. My mouth still waters to remember the "Schusterbroedchen" (shoemaker's rolls) served there, rye bread covered with fine flour. I used to enjoy hearing the student songs. I bought a book of such songs and became familiar with them. I liked particularly the traditional ones, dating from the medieval universities, and not peculiar to the Germans, like "Gaudeamus igitur" and "Integer vitae", and "The Pope, he leads a jolly life."

The room adjacent to ours in the Philipstrasse was occupied by Morris Karpas, an American studying psychiatry with Ziehen, then a famous name, now forgotten. One day in a fit of enthusiasm Karpas burst into my room and said: "Here, Ottenberg, is the most remarkable book I have ever seen; you must read it". It was the relatively new "Traumdeutung" of Sigmund Freud. The style was obscure, the German was difficult and after reading the first chapter, I gave it back to Karpas. In later years I read that and other books, and got to know something about psycho-analysis through my friend, C. P. Oberndorf, who founded the Mental Health Clinic at Mount Sinai in 1913, and A. A. Brill who translated Freud's works and introduced psycho-analysis into America. Freud, though some of his greatest work had already been done, was ignored in Berlin.

On Sundays we dined at a better restaurant, the Rheingold near Potsdamer Platz, and on gala occasions at Kempinski's on "Unter den Linden," or at the Hotel Adlon, where foreign visitors congregated. Once in a while we went to a play or a concert. These were extremely good, and by American standards extraordinarily cheap. The plays were mostly classics given by excellent stock companies. "The Merry Widow" and the "Dollar Princess" (a satire on America) were the reigning musical comedies. I am probably getting old and crochety, but it seems to me one does not hear such melodies in modern musical comedies.

The whole subject of expenses seems incredible to me now. I had \$1,365 for my trip and with it I crossed the ocean and studied for a year. My funds included \$500 from the Blumenthal Fellowship (which was renewed for a second year) and a loan from Libman (who made it easy to repay him by sending me laboratory work on his patients after I returned). My claim that I went so far on that relatively small sum, would make me regard myself as a liar if I did not know the facts. I was economical but not penurious. I enjoyed three excellent short vacations; the first was a walking trip during the spring vacation in the beautiful "Saechsische Schweiz" district near Dresden, along with A. A. Epstein and a talented young Italian doctor and his sweetheart, a beautiful Russian Jewess, a student of chemistry. The second vacation was in connection with my Vienna trip and consisted of a walking tour along with Epstein and another friend from New York. We tramped for a week with packs on our backs through the magnificent Dolomite mountains in the Tyrol, from Cortina to Bozen (now Bolzano). At one time we got lost on the way to Pordoihoch near

the Brenner Pass. We asked a shepherd for water but he would not even sell it to us, because he had to carry his entire supply from his home. Fortunately a heavy hail storm came up and we gathered hail stones and consumed them with sugar from our "Rucksacks." We did some perilous rock climbing, roped to a guide (up the Rosengarten Spitze) and we skidded in the loose snow down the face of the glacier into the lovely Pusterthal. For that trip we all joined the "Alpenverein" so as to take advantage of the huts scattered through the high mountains and stocked with refreshments and wine.

At the end of that trip Epstein and I went to Buda-Pesth to attend the first International Medical Congress (I still have on my desk a medallion given to all members of the Congress). There Jacques Loeb, (already a member of the



FIG. 2.  
BERLIN 1910

recently established Rockefeller Institute) created a tremendous sensation, by demonstrating for the first time artificial parthenogenesis by chemical means.

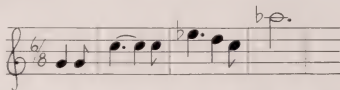
There was a revealing incident inseparably connected with my memory of Buda-Pesth. In Berlin Epstein had made the acquaintance of a young Hungarian chemist, assistant of Carl Neuberg. When he heard that we were going to Buda-Pesth, he said the Hungarians were the most hospitable people in the world, and he would not hear of our stopping at a hotel; we must be guests of his family. We called on them and were installed in their best bedroom. All went well until about 11 p.m.. Then we both got out of bed, bitten by innumerable members of the family to whom we had not been introduced. We lit the candles and sat up the whole night collecting specimens of *Cimex*. In the morning we were embarrassed for an excuse to make a get-away. We finally told the family that we saw we were putting them out of their best bedroom. However, we left our collection of dead bedbugs in the candle dish, and found a good room

in a little hotel at the foot of the castle. I have always wondered whether those kind people were so immune to bed bugs that they did not notice them.

The third trip made just before embarking for home from Genoa, was a sight-seeing tour in Italy, during most of which I was able to pass myself off as a German student from Berlin: German students got the lowest prices everywhere, Americans paid the top.

One of my most vivid memories is the First International Aeronautic Meeting held at Tempelhofer Field on the southern outskirts of Berlin. The field has since become famous in two wars. All the great pioneers flying took part in that competition, the Wright brothers, Curtis, and Bleriot (the first man to fly across the English Channel). Their flimsy open-seaters flew around the field a few hundred yards up in the air, and it was considered a great feat that they could stay up as much as an hour. The Zeppelin dirigible balloons (then considered much more promising than aeroplanes for the future), were also in evidence and occasionally were seen gliding over the city.

Automobiles also were then very new. There may have been ten or twenty in Berlin. There was one you could always identify. It was that of the last Crown Prince, then in the heyday of his career. You could tell it at a distance by his horn which did not honk a simple note, like the auto of an ordinary millionaire, but played a beautiful cornet melody, namely Wagner's Siegfried motif from the Walkure:



Everyone, of course, knew the words of the song, which might be translated into the American: "The greatest big-shot in the world."

The automobile on the accompanying picture post card of the Brandenburger Tor (a card sent by Bass to Oppenheimer then on vacation) might well have been that of the Crown Prince (fig. 2).

Philipstrasse was a short street. At one end it abuted on the Charité. At the other was a large "Kaserne" or barracks and drill yard. From our window we used to see the drilling and goosestepping, which gave a tremendous, and even then sinister impression of military power.

In spite of its importance as a center of culture, science and art, there was something bleak, unfriendly and harsh about the atmosphere of Berlin. The great numbers of military and police, and the universal distribution of "Verboten" notices gave an overall air of repression that was uncomfortable. I was standing one day on the rear platform of a street car (horse drawn) whistling quietly to myself. The conductor said: "Verboten. You can't whistle on the platform of a car. It's against the law." I subsided until I reached my destination. Then, as I stepped off, I whistled "the Marseillaise" loudly. He shouted something to me as his car disappeared. I think he understood.

I wish to thank Rubin, Bass, Epstein and Garbat for reminding me of some of the incidents.



## PRESACRAL NEURECTOMY IN INTRACTABLE DYSMENORRHEA

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S.

(Boston, Massachusetts)

The purpose of this paper is to report the results of presacral neurectomy for intractable dysmenorrhea, performed on 76 patients from December 4, 1933 to June 21, 1946. The nature and history of the disease will first be briefly reviewed and the technic of the operation described.

Dysmenorrhea, or painful menstruation, is a symptom and not a disease. It is referred to as primary when no gross anatomic lesions can be found to account for it, and as secondary when organic disease of the pelvic organs, or organs adjacent to them, is responsible for the pain. Pain may be slight, moderate, or so severe that the patient is incapacitated for a number of days each month.

A number of years ago physicians agreed that mechanical obstruction to the menstrual flux was the principal cause of the pain, according to the old saying, "*nulla dysmenorrhea nisi obstructiva*." From this belief resulted the various interventions applied to the cervix. These included dilatation, frequently followed by curettage; the insertion of cervical plugs, happily almost entirely abandoned nowadays because of the serious infection that may follow their use; and the cervical operations of Pozzi, Dudley, and the like, also given up in modern gynecology. The belief in endocrine disturbances as the etiologic factor was then substituted for the mechanical theory. Finally, and more recently, the efforts of those interested in the relief of dysmenorrhea have been directed to the pelvic sympathetic nervous system, which, it is believed, under hyperexcitability is responsible for intractable dysmenorrhea when no gross pathologic conditions can be discovered to account for it.

In either primary or secondary dysmenorrhea relief may be obtained in the milder cases by rest, the application of heat to the pelvis, and the administration of certain drugs and hormones. Analgesics are useful in the symptomatic treatment, since they relieve pain no matter what its origin. Some of the newer antispasmodics, by relaxing the uterine muscle, have proved of benefit, and among the hormones, progesterone, which also has a relaxing effect on the uterine muscle, has been of value. Dilatation of a tight cervix, one of the oldest procedures in use, and one that was almost invariably resorted to in cases of dysmenorrhea forty to fifty years ago, is still in use and gives surprising relief in a number of patients.

It is in primary dysmenorrhea of the intractable type that presacral neurectomy or resection of the superior hypogastric plexus finds its greatest field of usefulness. The results in a number of cases are dramatic, and young women who had previously been crippled each month by a dysmenorrhea that necessitated their remaining in bed one or more days may menstruate without pain after this intervention. This operation should, however, be resorted to only

in those cases in which all other simpler methods have failed, and should be reserved for the so-called "spastic" or uterine form of dysmenorrhea, a condition in which the patient experiences severe cramps. It is not intended for ovarian dysmenorrhea, since it has but little value in that condition. Although striking results are obtained in the control of menstrual pain by presacral neurectomy, one should refrain from applying it to women who may be relieved by the simpler forms of therapy.

As a matter of historical interest in connection with pelvic sympathectomy for dysmenorrhea, Jaboulay in 1898 and Ruggi in 1899 were pioneers in attacking the painful element, in this case the pelvic sympathetic nervous system. In 1921, Leriche proposed peri-iliac sympathectomy, and was followed by Cotte, Hallopeau, and Michon. The names of Latarjet, Hovelacque, Elaut, Bonnet, Fontaine, Hermann, Tiedeman, Learmouth, Braasch, and Kuntz should be mentioned in connection with pelvic sympathectomy for dysmenorrhea, since these observers played an important role in the development of the operation employed today. In 1925, Gaston Cotte proposed his own method of presacral neurectomy, which was such an improvement over those of his predecessors that it has remained the standard technic up to the present time.

#### TECHNIC OF PRESACRAL NEURECTOMY AS PROPOSED BY COTTE

In the Cotte operation, the patient, under suitable anesthesia, the bladder having been emptied and the abdominal wall prepared, is placed in the Trendelenburg position. Cotte advises an abdominal incision partly above and partly below the umbilicus. Unless the patient is very obese, I prefer the median pelvic incision, drawing the upper end of the incision upward by a suitable retractor. The intestinal mass is pushed upward and held by laparotomy pads, and the sigmoid is packed to the left with suitable pads, thus exposing the inter-iliac triangle. The peritoneum is opened in a superficial manner and is separated from the underlying areolar tissue,—(the cellulofibrous membrane of Cotte)—before it is incised. This layer of areolar connective tissue contains the sympathetic fibers and ganglia that make up the superior hypogastric plexus. The so-called cellulofibrous membrane is dissected from side to side and bunched toward the middle. (I have found the delicate Metzenbaum scissors to be an excellent instrument for this dissection.) In the course of this dissection the bifurcation of the aorta, the right common iliac artery and its bifurcation into the external iliac artery and the hypogastric artery, and the right ureter are exposed. On the left side the large common iliac vein is in evidence. The bundle of areolar tissue containing the sympathetic nerve elements is ligated 1 cm. above the bifurcation of the aorta and resected, the lower part of the resection being carried out considerably below the promontory of the sacrum, with the middle sacral artery exposed. The fasciculus of areolar tissue containing the nerve elements is resected to the length of 4 to 6 cm.

#### RESULTS

In this series of 76 patients, the ages ranged from 13 to 38 years. Fifteen patients were between 13 and 19 years old, 45 between 20 and 29, and 16 between

30 and 38. The results, which are based on the patients' voluntary reports,\* have been classified as satisfactory, improved and unimproved. The satisfactory cases were those in which pain following the operation was absent or barely noticeable. The improved cases were those in which the patients had pain for a short time but considered themselves greatly relieved. The unimproved cases were those in which there was as much pain subsequent to the operation as there had been before it. Follow-up was obtained in 68 patients (90 per cent), of whom 52 were examined in the office and 16 answered questionnaires. Of these patients, 40 (59 per cent) had satisfactory results, 19 (28 per cent) were improved, 8 (12 per cent) were unimproved, and 1 died during the operation.

Statistics covering the postoperative deliveries have not yet been compiled. One patient had two pelvic deliveries following operation, another had one pelvic delivery, and a third had a transverse cervical cesarean section.

In the single case with a fatal termination, Case No. 33, the patient was a girl 13 years of age, whose physical development corresponded to that of a young adult. Her dysmenorrhea was so severe that she had been incapacitated each month. She had been given analgesics and hormones without benefit, and she had had a previous dilatation and curettage by another surgeon, without relief. She was operated on under general anesthesia. When the abdomen was opened, the omentum and sigmoid were found to be adherent to the posterior surface of the fundus of the uterus. It was believed that the uterus had been perforated at the time of the dilatation and curettage, resulting in these adhesions. A presacral neurectomy was performed without any special difficulty. As the posterior peritoneum was being closed the patient expired. The death was classified as due to anesthesia.

#### SUMMARY

Presacral neurectomy or resection of the superior hypogastric plexus is a valuable measure in primary dysmenorrhea that is not relieved by simpler means of treatment. The technic of the operation is discussed, and the end results in a series of 76 patients receiving it are analyzed. This method, although delicate in execution, should offer no insurmountable obstacle to the well-trained pelvic surgeon.

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\* In operations for the relief of pain it is necessary to rely on the patient's account of the postoperative result, since there is no objective method that can be employed. It should also be borne in mind that many patients treated for intractable dysmenorrhea must be classed as psychoneurotic.

## PSYCHIC ASPECTS OF JUVENILE AND ADOLESCENT DIABETICS

HERBERT POLLACK, M.D.

(*New York, N. Y.*)

Before the introduction of insulin, diabetes in the child was invariably fatal within a year of its onset. As insulin became available, it became possible to observe young adults who have grown through childhood and adolescence with insulin-treated diabetes, and it became apparent that children and adolescents with the disease may look forward to normal growth and development, differing little from non-diabetics.

A diet which will meet growth needs is important to ensure full development of the child diabetic. In the early days of insulin therapy for the child, when diets were restricted, dwarfism was quite common as were delayed menses. These developmental defects have virtually disappeared with increased knowledge of the importance of diet. Even since 1936, when protamine zinc insulin was introduced, remarkable improvements in growth, development, and endocrine development in insulin-using children have been noted. Young females who had never experienced menses because of the diabetes in many instances have entered upon normal menstrual cycles.

Children from the ages of five and six often take the entire responsibility for their insulin dosage. They learn to use the needle very quickly and easily grow accustomed to it. The young diabetic should be taught to live with the disease, thereby avoiding in him any psychic maladjustment. Some emotional reactions of the child to his disease become immediately obvious. Among them are: temper tantrums, lack of desire to eat, stubbornness, bed-wetting, aggressive play habits, and other similar manifestations. Their relationship to strict discipline in the child's regime are not readily understood by the parent.

It is, of course, essential that the physician should emphasize strict adherence to the diet and fixed routine, as this will keep the diabetes in equilibrium. But he must bear in mind the dangers which may arise from the too vigorous application of therapeutic regimes to children, and the likelihood of an unexpected rebellion of the child against the routine, either directly or by dint of subterfuge. Personality problems or neurotic symptoms may present themselves as new and unwelcome developments.

The risk of arousing personality or neurotic problems should not influence the treatment of immediate and severe diabetic symptoms; still, during the course of the therapy directed against the immediate symptoms, the physician can take precautions against those more remote results of the child's regime. Several fortunate circumstances work in favor of the physician. Through the dramatic efficacy of his treatment, he can prove to the parents and the child his ability and his willingness to help. Furthermore, neurotic difficulties which are secondary to organic disturbances often respond more easily to simple corrective

measures than do those which are of an essentially psychogenic nature (neuroses unrelated to such organic disturbances as diabetes).

In order that the child's illness shall have as little disrupting influence on his emotional life as possible, the physician may use one of several approaches. The child must always be made to feel that he is an adequate individual, capable of being accepted and loved. This reassurance must come constantly from both parents; never must they blame themselves for the offspring's condition, nor must they look upon him as defective. So long as the parents can be made to feel that they are contributing to the child's improved condition, it will usually be more simple to bring forth this reassurance. Many parents begin their relations with the doctor with the expectation that they will be blamed for difficulties which may arise in the handling of the child. If their fears in this regard are confirmed, they are liable to develop subtle resistance to the physician's efforts. Other parents elevate the physician to a godlike, omnipotent position; of course, they bitterly resent his inevitable inability to maintain such a role.

The greatest protection to the child's inner feeling of strength comes from his active participation in the treatment of his condition. Under proper supervision and leadership, he should be encouraged in doing for himself all things which can be safely left in his hands. He should have an active part in the calculation of his diet and his insulin dosage, for instance. The feeling that he, personally, is playing a part in the control of his diabetes has a very beneficial psychological effect.

The child should also be encouraged to indulge in all the play and normal activity which his regime allows. Here the physician encounters resistance, in many cases. Parents tend to be overanxious, overprotective, and oversolicitous toward a child who, they feel, is different from normal children; they must therefore be made to understand that the child gets much more satisfaction, gets a definite sense of security and independence, from doing things for himself. If he is denied these things by being made to feel utterly dependent on others, he develops into the "spoiled child" who cannot help using "magical" symptoms designed to force those around him to care for his needs and wants. It is therefore not the excessive parental affection or giving which is the danger; rather, it is the weakening of the child's individual strength, ability, and initiative through the smothering of his activity.

There is, apparently, a need for a biologically conditioned level of instinctual gratification in each child. Therefore to a certain extent, his instinctive reactions toward some situations, facts, and conventions must be catered to. This required gratification may be disturbed seriously by the restrictions placed on the child's dietary habits during the treatment of the diabetes. For this reason special attention should be paid to the likes and dislikes of the young patient—so far as this is possible within the framework of necessary treatment. It may even be desirable to make provision for occasional parties where the child can enjoy the same fun as do his friends. Insulin-covering of the addi-



tional food can be arranged. This would be impossible if the child were forced to cheat on the diet, as occasionally happens when such provision is not made.

Since the diabetic child inevitably must be subjected to a certain degree of constant frustration, it is essential that no disciplinary measures involving further restrictions be employed. These do not work; they simply set up vicious cycles in which punishment becomes an aim of the child's behavior rather than a corrective measure. Almost any child tends to conform to rules and regulations which it feels are dictated by love and affection, and by the real needs of the situation.

If the particular child is consistently rebellious in his attitude, it is a sign that psychological maladjustments are already present, and necessary steps will have to be taken. Proper supervision, adequate planning, suitable companionship, and effective leadership will have a much more beneficial effect than any physical or mental chastisement.

If a child develops deeper neurotic trends, disturbances of the eating process or of the urinary function, or organically induced anxiety-states, all or any of these may become fixed to other emotional factors—new symptoms, not directly connected with the diabetic symptoms, may ensue. In such cases more active psychotherapy may have to be added to the antidiabetic treatment.

## UTEROGRAPHY AS AN AID IN THE DIAGNOSIS OF UTERINE BLEEDING

SAMUEL A. ROBINS, M.D.

(*Boston, Massachusetts*)

Menorrhagia and metrorrhagia are symptoms which are often disturbing to the patient and perplexing to the physician. Every available method should be promptly employed to determine the exact cause of the bleeding in order to ensure proper treatment. A complete history, bimanual examination, curettage, and biopsy are regarded as the traditional diagnostic methods of choice, yielding a high percentage of accuracy. Likewise, uterography may frequently add valuable information of diagnostic significance. Since, in our opinion, this procedure is simple and in properly selected cases harmless, it should be used more frequently.

### HISTORICAL REMARKS

The evolution of uterography began when I. C. Rubin published his paper in 1914 on "The Value of Collargol to Outline the Uterus." The following year he published another paper on "X-ray Diagnosis in Gynecology with Aid of Intrauterine Collargol." In 1914 an article appeared by N. H. Carey on "The Injection of Collargol to Determine the Patency of the Fallopian Tubes."

It was a visionary and stimulating thought of Rubin to open up this important field of gynecological roentgenology. In his paper published in *Surgery, Gynecology and Obstetrics* in April 1915 he said: "The idea of employing the x-ray for diagnosis in gynecology is obvious in view of the multiple uses to which this agency is put in other specialties."

Later, Rubin and other investigators tried sodium bromide, thorium citrate, and bismuth paste to outline the uterine cavity and tubes. All these media, however, were unsatisfactory, because of severe reactions and inadequate radiographic contrast. Then came the era of lipiodol. This iodized oil was originated by Lafay in 1902. The preparation is stable, nonirritating, and nontoxic; it is well tolerated by the peritoneum and other tissues. This excellent radiographic medium was accepted by many investigators, including Rubin. By 1922 suitable radiographic media established gynecography as a definite diagnostic procedure. Since that time other types of iodized oils as well as water-soluble opaque media have been used. There also have been many other refinements in the technic and diagnosis. The iodized oils are still the media of choice.

### TECHNIC

The patient is instructed to take a cathartic the night before and a cleansing enema on the morning of the examination. She is placed on a table equipped with a Bucky diaphragm and stirrups. Preliminary to the instillation of the iodized oil into the uterine cavity a scout film of the abdomen should be taken. The plain film may reveal numerous pathologic conditions and is often a valuable diagnostic adjunct. Rounded, ovoid, or irregular dense shadows which produce pressure defects on the partially filled bladder immediately suggest uterine enlargement or fibroid. Occasionally these soft-tissue masses may contain small or massive irregular calcifications such as sometimes occur in fibroids. Areas of increased density high in the pelvis without changes in the contour of the bladder suggest ovarian tumors. Teeth and bony structures in the pelvis will lead to the diagnosis of dermoid cyst or teratoma. A rounded mottled area of increased radiance surrounded by a dense ring is pathognomonic of a dermoid cyst without calcification (Robins and White). Feathery

scattered calcific bodies associated with a pelvic mass are diagnostic of papillary tumors of the ovary (Lengley). Occasionally skeletal outlines may be found, indicating an early pregnancy which was not suspected. Foreign bodies such as needles, pencils, and sponges have been unexpectedly found in the uterus, vagina, bladder, rectum, or soft tissues.

Following the inspection of the flat film the patient is placed in the lithotomy position. The vulva is scrubbed. A fiber bivalve speculum with light attached (Cameron) is introduced and the cervix exposed. The upper portion of the anterior lip of the cervix is grasped with a tenaculum about one-quarter inch above the external os. The mucus usually present in the cervical canal must be completely removed by suction. The iodized oil is then introduced through the Robins cannula with manometer attached. The injection is made slowly and gradually, observing the pressure. In the patients with a history of abnormal bleeding, the pressure must not exceed 150-180 mm. of mercury. Excessive pressure may cause intravascular penetration, particularly in the presence of erosions or ulcerations. The entire procedure must be painless. Pain is a danger signal, and the injection must be stopped regardless of the pressure and the amount injected.

M. N. Hyams was the first to suggest "the interrupted fractional injection," which is a definite refinement in the technic to demonstrate small intrauterine lesions. This method consists of the injection of fractional amounts of the opaque medium (1-2 and 4 cc.) into the uterine cavity. Films are taken after each injection. In our laboratory the uterine cavity is then completely filled and stereoscopic films are made.

#### INDICATIONS FOR UTEROGRAPHY

The causes of menorrhagia and metrorrhagia are numerous. The following conditions causing abnormal bleeding have been clearly and satisfactorily demonstrated by uterography:

- Polypi { Endocervical
- { Endometrial
- Uterine fibroids { Intramural
- { Submucous
- Hyperplastic endometritis
- Endocervicitis
- Retained products of conception
- Hydatidiform mole
- Ectopic pregnancy
- Ovarian tumors
- Adenomyosis
- Carcinoma

#### POLYPI

Polypi may be present in the cervical canal or in any portion of the uterine cavity. They may be small or large, single or multiple, pedunculated or sessile. Gynecologists realize that a uterine polyp occasionally may be left behind after careful curettage, which may cause persistent uterine bleeding. Following a preliminary diagnostic curettage and after a hysterectomy pathologists have found single or multiple polypi in the pathological specimen. This is especially true of polypi in the fundus and in the cornual portions of the uterus. A sessile type of polyp is most often the offender.

Roentgenographically polypi usually appear as small or large sharply outlined filling defects, ordinarily not distorting the normal shape of the uterine cavity. The sessile type may produce slight irregularity at its attachment, especially

if it is situated near the lateral borders or fundus. These small tumors are best demonstrated by the fractional method of uterography, since when the



FIG. 1. Small polyp in lower portion of uterus just above internal os



FIG. 2. Small sessile type of polyp at the fundus near the left cornu

cavity is completely filled with the contrast medium such defects may be obscured (figs. 1 and 2).

## FIBROIDS

Fibroids of the submucous or intramural variety are readily demonstrated by uterography. They may be small or large, single or multiple. They appear as pressure or filling defects, depending upon their location. They distort the uterine cavity. The degree of distortion depends upon the size of the tumor.

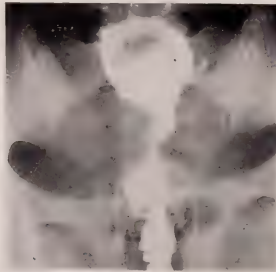


FIG. 3. Submucous fibroid

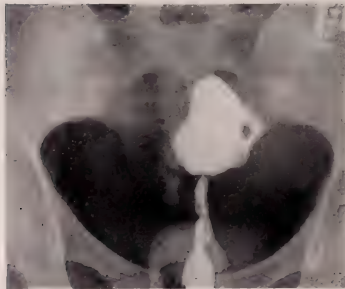


FIG. 4. Intramural fibroid. Note small polyp near the right cornu.

As a rule the uterine cavity is enlarged and the cornual portions may be rounded. Large pressure defects may be seen at the fundus, giving the appearance of a bicornuate uterus. There may be pressure defects on the lateral walls of the uterus. Fibroids may encroach upon the cervical canal, which may cause elongation and displacement. Occasionally small fibroids cannot be differentiated from large polypi (figs. 3 and 4).

## HYPERPLASTIC ENDOMETRITIS

This condition can frequently be demonstrated by uterography. The uterine cavity is generally enlarged; the borders are wavy, irregular, and hazy due to



the prominent folds of the hypertrophied endometrium. In advanced cases, the cornual portions of the uterine cavity are slightly irregular and rounded.

#### ENDOCERVICITIS

The roentgenographic picture of endocervicitis is characteristic. The cervical canal is widened and the walls present a serrated feathery appearance due to enlargement of the Nabothian glands, small ulcerations of the endocervix, or both (fig. 5).

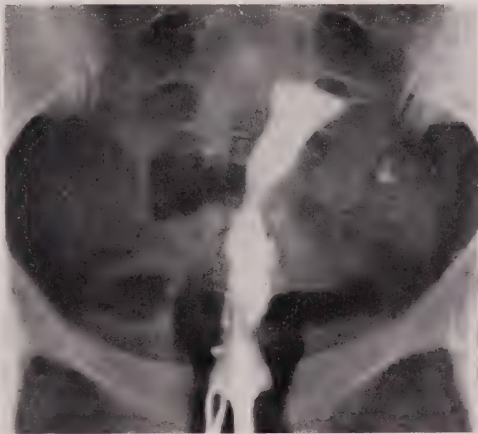


FIG. 5. Endocervicitis. The cervical canal is dilated. The striae are well marked on the lateral walls of the cervix.

#### RETAINED PRODUCTS OF CONCEPTION

The uterine cavity is grossly enlarged but regular in contour. The lower uterine segment is widened. There is also widening of the cervical canal. Within the cavity, there are numerous filling defects which have a bizarre appearance, due to the presence of varying amounts of retained placental tissue, necrotized material, and coagulum. At times this condition is difficult to differentiate from submucous fibroids (fig. 6).

#### PREGNANCY

When pregnancy is suspected, patients may present themselves with persistent staining or bleeding, with or without associated pelvic pain. In these cases it is essential to differentiate an intrauterine pregnancy, extrauterine pregnancy, extrauterine pregnancy, or hydatidiform mole.

The gynecologist may frequently make a correct diagnosis from the clinical history, physical findings, and laboratory tests. However, some of these cases are diagnostic problems which may be solved by uterotubography.

The diagnosis of early pregnancy can be readily made by this method, when cautiously employed. The uterine cavity is enlarged and atonic. The opaque medium should enter freely under low pressure. The uterogram will present a "curved shelving" above the level of the internal os. The iodized oil, flowing gently between the amniotic membranes and uterine wall, displaces the sac and its embryonal contents; thus a filling defect is produced on the x-ray film. The iodized oil may pass through one or both tubes.

In the normal pregnancy abortion is very unlikely to result. This was

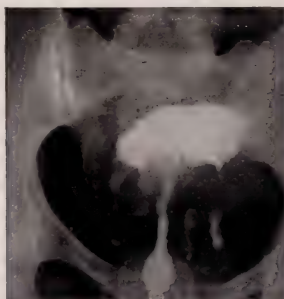


FIG. 6. Retained products of conception

decisively proven by Heuser and many other observers, who were unable experimentally to institute abortion by this method.

In extrauterine pregnancy the diagnosis is more difficult. The demonstration of a trumpet-shaped shadow at the distal end of the tube is diagnostic of this condition. In suspected cases tubal pregnancy can be definitely ruled out if both tubes are patent.

We do not recommend this procedure as a routine measure because of the remote danger of abortion in intrauterine pregnancy and the danger of rupturing the tube in tubal pregnancy. In all such cases where uterotubography is employed we must emphasize that the contrast medium must be introduced under controlled low pressure without trauma.

#### HYDATIDIFORM MOLE

The roentgenologic diagnosis of this lesion is not difficult. The uterine cavity is enlarged and its outline is irregular, showing multiple circular areas of diminished density arranged in grape-like clusters.

## OVARIAN TUMORS

Ovarian tumors may often be mapped out by the iodized oil when films are taken twenty-four hours after the injection. They are seen as ring-shaped shadows surrounded and outlined by the opaque medium which entered the pelvic cavity through the patent tubes. When large, these tumors may be seen to displace the uterus and the corresponding tube (figs. 7 and 8).



FIG. 7. Lower portion of the left tube is displaced by a small ovarian mass.

## ADENOMYOSIS

The diagnosis of adenomyosis as a cause of uterine bleeding is rarely made clinically. In the past few years I have observed a number of cases in which uterograms were performed because of bleeding where the roentgenographic diagnoses of adenomyosis were made. Six of these cases were proved pathologically.

The radiographic appearance of adenomyosis is characterized by single or multiple penetrations of the opaque medium into the uterine wall, forming sinus-like tracts varying from 3 mm. to 2 cm. in length. The lesion may be generalized or localized in one portion of the uterus. This pathologic entity is usually associated with uterine enlargement and fibroids.

To the best of my knowledge, this new roentgen sign was never previously described. A more complete paper on the subject is now in preparation (fig. 9).

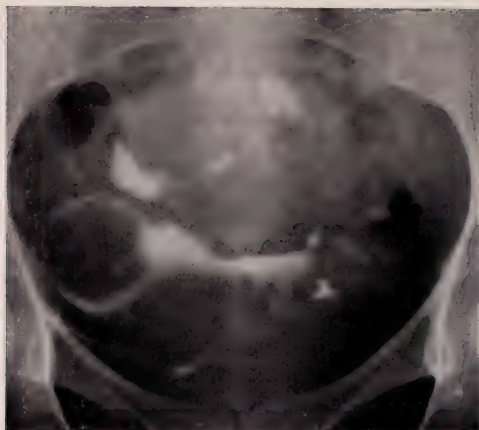


FIG. 8. Same case. Note the ovary mapped by the lipiodol forty-eight hours after the injection.



FIG. 9. Adenomyosis (focal) associated with fibroid. The small penetration at the right lower border of the uterus is pathognomonic of this condition.

## CARCINOMA OF THE UTERUS

In this condition, only moderately advanced and extensive lesions can be demonstrated if the cervical canal is not obliterated. Uterography is of no value in early lesions where only the endometrium is involved. We, therefore, do not recommend it as a diagnostic agent of suspected early malignant infiltration. Once the diagnosis is established by other means, uterography is of great value for showing the extent of the lesion.

In the literature one can find considerable controversy as to the danger of



FIG. 10. Extensive carcinoma of the uterus associated with fibroid. Patient aged 42.

dissemination of cancer cells into the pelvis by the injection of the iodized oil into the uterine cavity and through the tubes.

The radiographic appearance in advanced carcinoma of the cervical canal and uterus is pathognomonic. The uterine cavity is not markedly enlarged, and presents a localized irregular mottled defect with hazy and slightly irregular borders. The normal contour of the uterine cavity is interrupted. The extent of the infiltration can be readily determined. It is my opinion that careful injection of the opaque medium into the uterine cavity under low pressure is without danger of transplanting malignant cells. I feel certain that this procedure is less likely to cause dissemination of cancer cells than that of diagnostic curettage (fig. 10).

## CONTRAINDICATIONS

Uterotubography should not be performed in the presence of:

1. Acute inflammatory disease of the pelvis



2. Purulent discharge from the cervix
3. Massive hemorrhage

#### CONCLUSIONS

Uterography is an accepted and safe method of gynecological examination in abnormal uterine bleeding. It often aids in establishing the cause of such bleeding and this may lead to proper therapy. The technic has been described and the contraindications mentioned. Because of its simplicity and safety it should be employed more frequently in cases of obscure uterine bleeding. The uterographic evidence should be correlated with the clinical manifestations.

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## RADIUM THERAPY IN BENIGN UTERINE BLEEDING

A. J. RONGY, M.D.

(*New York, N. Y.*)

At the meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in 1942 I presented an analysis of the results of radium therapy in benign uterine bleeding, based upon a study of 350 cases. Since then 118 cases have been added to the list.

At that time I stated that this particular clinical study of the results obtained differs measurably from the methods commonly employed in the evaluation of the efficacy of a therapeutic agent in the treatment of disease. Ordinarily, studies of large series of cases, emanating from clinics, represent the work of a number of surgeons in both private and ward patients. Usually the subjective and objective symptoms are recorded by junior members of the staff. The decision for a given procedure therefore represents the judgment of many surgeons. The subsequent history and final result are collated and tabulated by members of the staff, who often do not have an intimate knowledge of the medical and psychological status of the patient from the inception to the termination of treatment.

This series of 468 cases, covering a period of 18 years, consists of private patients, selected from a large number of women who sought medical advice because they suffered from vaginal bleeding and associated symptoms. Each patient was first seen in the office. The history, the physical examination, the indications for the use of radium, post-operative course, the morbidity and complications, the subsequent history, and the final results were evaluated and recorded by me. This method of procedure left no room for misinterpretation or improper evaluation of the results obtained.

It is needless to state that this series of cases represents a definite departure from the radical practices usually followed by gynecologists in the treatment of uterine bleeding of benign origin, who subject these patients to abdominal or vaginal hysterectomy and dismiss the irradiation treatment from their medical armamentarium. Obviously, many gynecologists fail to recognize the modern surgical concept that the treatment of any pathological condition must be accompanied by the least mutilation of organs.

It cannot be denied that the average woman is less disturbed by menopausal symptoms when she knows that no organ has been removed, that the uterus and ovaries are still intact, than when menopause is induced by extirpation of the genital organs. The husband, too, is less likely to have his sexual life upset when he realizes that the uterus and ovaries are still present and that his mate is simply undergoing menopausal changes, and views it as a normal physiological process which he expected to take place sooner or later. This important phase of the marital state is not given serious consideration by the average gynecologist.

Curiously enough, European gynecologists utilized irradiation therapy

extensively long before it was adopted in the United States. Radiation for the treatment of fibroids took precedence over surgery in important European clinics. In the United States leading gynecologists in large medical centers, according to all reports, still treat 95 per cent of all fibroids by surgery and only 5 per cent by radiation. This definitely indicates the general trend in the treatment of fibroids and uterine bleeding in this country. It is my firm belief that the time has come when gynecologists should reevaluate their procedures in the treatment of uterine bleeding of benign origin.

The symptoms that primarily impel the patient to seek medical advice are 1) abnormal vaginal bleeding, 2) pain in the lower portion of the abdomen, 3) pressure in the pelvic region. The cardinal symptom is profuse or irregular bleeding, which may or may not be accompanied by pain or pressure, disturbed micturition, or other symptoms.

Current medical literature discloses a glaring lack of differentiation in the treatment of benign uteropathies. There is an absence of proper interpretation of the etiologic factors producing these symptoms. The pelvic findings, the general constitution of the patient, her marital and social status, should form an all inclusive medical picture, which would bespeak either a radical or conservative procedure for the control and cure of the symptoms.

Gynecological pathologists are still groping in the dark as to the cause and origin of uterine bleeding. Even its mechanical process is not clearly understood. Disturbed vascularization of the endometrium requires further elaboration and clarification. This is also true of the cause and origin of uterine fibroids. In 1901, Roberts stated tersely: "Nothing is known as to the cause of fibroids." Forty years elapsed and in 1940 Novak did not shed more light when he stated: "Little or nothing is known as to the underlying cause for the development of uteromyoma." The hormonal factor or the local mechanical disturbance of the myometrium do not fully account for the bleeding or oozing from the uterus in a goodly number of cases. It is a well known clinical fact that women may have large fibromyomata of the uterus without the slightest disturbance of their menstrual function. Again, the uterus may be normal in size and position and yet bleed profusely. Even the microscopic study of the endometrial tissue often does not help to clarify the pathological process. The microscopic examination of the endometrial tissue in this series of cases disclosed a resting endometrium in about 39.3 per cent and a hyperplastic endometrium in about 45.6 per cent. Obviously, it is difficult to explain bleeding in the presence of a resting endometrium or the presence of an endocrine imbalance without causing some change in the lining of the uterus. Furthermore, it is difficult to explain why a simple curettage may cure bleeding of endocrine origin. These are definite problems for the clinician and require further elucidation.

It is superfluous to state that the management of uterine bleeding, whether by conservative or radical methods, is still of an empirical nature. The occasional patient who may temporarily be relieved by organotherapy is the exception to the rule. Furthermore, it is dangerous to institute treatment for uterine bleeding before a microscopic study of the endometrium has been made, for in 12 patients

corpus carcinoma was discovered only after the curettings were examined microscopically, and in one case sarcoma of the body of the uterus was found. In none of these patients was malignancy suspected, nor had they given symptoms which would warrant the slightest suspicion of it. Had these patients been treated with deep x-ray therapy or organotherapy, an early malignancy of the corpus uteri would have been overlooked.

The following two cases are typical illustrations.

*Case 1.* Mrs. M. F., a physician, 50 years old, consulted me 8 years ago because she suffered from pain in the lower portion of the abdomen and slight menorrhagia. On examination the uterus was found to be enlarged to about the size of a ten weeks' pregnancy, containing a number of small fibroids. She gave a history of having had a coronary occlusion the year before. She was obese and a poor surgical risk. She was kept under observation and examined regularly every three or four months. Four years later she began to complain of irregular bleeding and upon examination the uterus was found to have increased in size. In view of her past medical history and because of her excessive weight, it was not deemed advisable to subject her to a major abdominal operation. Intra-uterine radiation was decided upon. When the cervix was dilated, necrotic material escaped and much necrotic tissue was removed by the curet. This patient had been observed for nearly five years. Her menstrual function had not been much disturbed. There was ample opportunity to observe any change in the symptoms, either of a local or constitutional nature. There was not the slightest indication of the development of malignancy. When the cancer cell actually superimposed itself upon the fibroid uterus could not be definitely established.

*Case 2.* Mrs. F. L., 30 years old, married 11 years, para II, youngest child 7 years of age, consulted me on September 15, 1923, because she had not menstruated in 7 months, and then began to spot and stain irregularly for one year. A tentative diagnosis of missed abortion was made and she was curetted. Microscopic examination of the removed tissues confirmed the diagnosis. Two years later she consulted me because she had been staining irregularly for six months. She had gained a great deal of weight, weighing 236 lbs. Her blood pressure was 240 systolic, 136 diastolic. On vaginal examination a small intramural uterine fibroid could be felt. A diagnostic curettage was performed and the bleeding proved to be of non-malignant origin. This was followed by deep x-ray therapy. The patient felt well, except for menopausal symptoms. On January 15, 1936, 11 years later, she began to complain of irregular spotting and staining. Vaginal examination disclosed a uterus which had undergone involution and was freely movable; the adnexae were apparently normal. She was again curetted and the endometrial tissue removed was grossly suggestive of carcinoma and was confirmed by microscopic examination.

The problem in the treatment of uterine bleeding is: When should a hysterectomy be performed or when should radium be used? Theoretically, clinicians should have no difficulty in arriving at a proper decision if they are not delimited in the management of this problem by a particular method of treatment. The size of the uterus, the location of the tumor—whether it is intramural, subperitoneal, or intraligamentous—are important factors in the treatment of these patients. The clinical findings must be evaluated in each patient, not only from the standpoint of curing the symptoms but also as to the safety of the procedure. There is no justification for subjecting a middle aged woman, suffering from idiopathic uterine bleeding or bleeding caused by intramural fibroids, not larger than the size of a three months' pregnancy, to a major surgical pro-

cedure, especially when there are definite constitutional contra-indications. A vaginal or an abdominal hysterectomy in such cases is not only a dangerous but a mutilating operation.

Patients suffering from submucous, subperitoneal, or intraligamentous fibroids, whether small or large are not proper subjects for radium therapy. Necrosis and infection of the submucous fibroids often follow radiation. A tumor that projects into the uterine cavity is easily discernible by the curet. The uterine surface is uneven, causing a zig-zagging of the curet in its upward and downward strokes. Radiation is definitely contra-indicated in all cases of uterine bleeding, who give a history of having had a pelvic infection or in whom pelvic adhesions may be suspected because of previous abdominal operations.

However, no matter how cautious one may be, it is often difficult to ascertain clinically the presence of an insidious infection in the genital organs, as illustrated by the following case.

*Case 3.* Mrs. E. W., 48 years old, had one child 19 years ago, consulted me on September 15, 1945, because she had been spotting and staining irregularly between menstrual periods. Vaginal examination disclosed a hard and nodular uterus, freely movable, and there was no apparent adnexal involvement. She was curetted and radium was inserted on October 2. Very little endometrial tissue was removed by the curet. Three days later she had a severe chill and a temperature of 106°F. The abdomen became distended and markedly tender. Her symptoms became progressively worse. The chills continued daily and the pain in the abdomen became accentuated. A few days later vaginal examination disclosed a large mass in the left cul-de-sac, extending into the abdomen and nearly reaching the umbilicus. The patient was confined to the hospital for twelve weeks, having an unusually stormy convalescence, and lost a great deal of weight. At no time during her stay in the hospital was it deemed advisable to subject her to a major surgical procedure. Finally the temperature began to subside and for two months after she left the hospital she was confined to bed at her home, running a low grade fever. However, the inflammatory mass finally subsided and the patient is now completely recovered.

One other patient in this series of cases developed a pelvic infection following the use of intra-uterine radiation.

As far as could be discerned, there was no damage to the abdominal viscera following radiation in this series of cases, though such occurrences are reported by reliable clinicians, nor did any of the patients develop colitis. These patients were closely observed at regular intervals and none gave symptoms, which would lead one to suspect injury to the gastrointestinal tract.

#### UTERINE BLEEDING ASSOCIATED WITH ESSENTIAL HYPERTENSION

There is a prevailing opinion among clinicians that hypertension is a contra-indication for abdominal hysterectomy. My experience differs in this respect. Patients suffering from essential hypertension, not accompanied by myocardial disease or obesity, hardly assume an immediate additional risk in undergoing a major pelvic operation. Convalescence is seldom complicated by the hypertension. Furthermore, they are less prone to develop emboli. As a rule it is not advisable to use radium in these patients because of its acute effect on ovarian function. Hysterectomy can be performed without removing the ovaries, so



that the patient will have the benefit of some ovarian function for one or two years.

Notwithstanding the limitations enumerated above for the use of radium in uterine bleeding, associated with fibroids, I am certain that 25 per cent of these patients can be cured with radium, who otherwise would be subjected to abdominal hysterectomy, and that in 40 per cent vaginal hysterectomy can be avoided.

#### UTERINE BLEEDING ASSOCIATED WITH VAGINAL AND CERVICAL LACERATIONS

Many patients, who suffer from uterine bleeding, require pelvic repair. Abdominal hysterectomy, without repairing the pelvic structures, often aggravates the relaxation of the vaginal vault and not infrequently leads to its complete eversion, a most troublesome complication and extremely difficult to repair. Again, vaginal hysterectomy, without reconstruction of the pelvic floor, is definitely an incomplete surgical procedure. Until recently, for some unexplainable reason, repair of the vaginal vault was seldom undertaken simultaneously with intra-uterine radiation. It was presumed that the healing power of the repaired structures would be affected by the radium. The fact is that the healing process is not at all interfered with by the presence of radium in the uterus. In this series nearly 100 patients had plastic operations on the cervix and the vaginal vault. In a considerable number the interposition operation was performed. The morbidity was not increased, nor the stay in the hospital prolonged. The application of radium in conjunction with repair of the vaginal vault proved more satisfactory than any other surgical procedure heretofore used. I believe it is to be the method of choice and that in the future it will supplant other surgical measures. Neither abdominal nor vaginal hysterectomy compares favorably with it.

#### DOSAGE

When I first used radium therapy for uterine bleeding, the number of CMH of radium required in middle aged women to bring about the cessation of menstruation was not definitely settled. The age and the dose were not properly correlated. This led to some confusion and opinions varied as to the amount of radium the average patient needed to accomplish a cure. I, too, varied the dose from time to time and finally arrived at the conclusion that 1,800 CMH is the appropriate dose for women 40 years or older. The concentration of the dose is important. Twenty five mg. left in the uterus 72 hours is preferable to 50 mg. left for 36 hours or 100 mg. for 18 hours. Nausea and radium burns are less likely to occur when the smaller dose of radium is utilized for a greater number of hours.

#### MORBIDITY AND POSTOPERATIVE COMPLICATIONS

Curettage and intra-uterine insertion of radium should theoretically not be accompanied by morbidity or mortality. Occasionally the patient will complain

of cramp-like pain in the lower part of the abdomen, induced by the foreign body in the uterus. The slight nausea which may occur as a result of the ray absorption is easily controlled. The average stay in the hospital is about four to five days.

Leucorrheal discharge in a small per cent of the patients will become more profuse for about two or three weeks and subside as soon as the debris in the uterus is completely expelled. Vesical disturbance is occasional. It is usually an exaggeration of an existing complaint, brought about by childbirth injuries. In my experience, extreme vesicular irritation, caused by intra-uterine radiation, does not occur as frequently as is generally ascribed to it, especially if the vagina is snugly packed with iodoform gauze and the bladder is not permitted to become overdistended while the capsule of radium remains in the the uterus.

#### MENOPAUSAL SYMPTOMS

It is clinically well established that the menopause syndrome does not manifest itself alike in all women. It differs in various ethnic groups and social classes. The factors influencing or modifying it are still not well established. It is still a moot question which of the specific organs are responsible for the symptoms. The most careful clinician is not always able to differentiate the organic from the psychologic manifestations. Norris and Behney found that menopausal symptoms following intra-uterine radiation occurred in about 95 per cent of cases. In this series 52.7 per cent had no or only mild flushes, about 39 per cent had moderate, and they were severe in about 7 per cent.

#### INVOLUTION OF THE FIBROID TUMOR

In 81 per cent, complete involution of the mass occurred, partial in 16 per cent. In a number of patients, whose bleeding was of idiopathic origin, the uterus atrophied to subnormal size. In a large number of patients hardly a trace of the fibroid could be elicited by clinical examination at the end of 18 months. The uterus felt hard as a result of the newly formed connective tissue.

#### POSTRADIATION PAIN

Many patients complain of some localized pain in the lower part of the abdomen during the involutional process of the fibroid. The pain, however, is never severe and gradually subsides as the fibroid involutes.

Six patients failed to respond to radium therapy. They continued to bleed irregularly and at times profusely. Panhysterectomy was finally performed in 4 of these patients. Two patients required supplemental x-ray therapy and in 2 radium therapy had to be repeated. One patient, who had 2 applications of radium, developed carcinoma of the cervix and body of the uterus 5 years later. One patient, at the age of 50, began to menstruate regularly after a complete cessation of menstruation induced by radium 12 years before. Another patient began to menstruate after an interval of 5 years. She became pregnant and aborted in the third month.

## SUMMARY

1) Curettage and intra-uterine radiation can be safely utilized in at least 35 per cent of patients, suffering from uterine bleeding. It should replace abdominal hysterectomy in about 25 per cent of cases and vaginal hysterectomy in 40 per cent.

2) The average dose required to induce artificial menopause in a middle aged woman is 1,800 CMH of radium. A capsule of 25 mg., remaining in the uterus 72 hours proved most satisfactory.

3) Complete involution of the tumor took place in over 80 per cent of the cases. Six were not affected by radium.

4) Radium is usually contraindicated in patients in whom the uterus is enlarged to more than 14 weeks of pregnancy or when a submucous fibroid is suspected. Its use should not be advised in subperitoneal or broad ligament fibroids.

5) It is dangerous to use radium in patients who give a history of having had a pelvic infection.

6) The menopausal syndrome is not accentuated by radium.

7) A leucorrheal discharge may appear for about 6 to 7 weeks in a goodly number of cases.

8) Sexual relationship is less likely to be disturbed, following the use of radium. The libido is usually not affected.

9) Curettage and insertion of radium should be performed by the gynecologist, not the radiologist.

Finally, I do not wish to convey the impression that I am especially interested in the treatment of uterine bleeding with radium. I have a deep interest in gynecological surgery, but these cases were selected from a large number of patients, who consulted me for uterine bleeding. I resorted to radium therapy only in those patients, who had a definite contra-indication to a major surgical procedure or when the fibroid was so small that there could be no doubt of a favorable result. I am convinced that a therapeutic agent which helps to reduce the morbidity and mortality in any pathological lesion, should not be ignored and should be made a part of the medical armamentarium.

## FETAL MORTALITY ASSOCIATED WITH CONSTRICTION RING DYSTOCIA

M. PIERCE RUCKER, M.D.

(Richmond, Virginia)

The literature dealing with the subject of uterine rings has two characteristics, (1) a great disagreement as to terminology, and (2) an unanimity as to the associated fetal mortality. It is to the latter that I direct my remarks at this time. All writers note a greatly increased fetal mortality, but none has attempted to evaluate the causes for this mortality. Clifford White, who was the first to differentiate clinically contraction ring or constriction ring from retraction ring, reported a fetal mortality of 63 per cent in vaginal deliveries and 42 per cent in cases treated by laparotomy. In fairness it should be said that many of the sections were done many years ago, before the refinements of the modern operation were in use. Harper states that the dangers to the child are those of intrauterine asphyxia from continued pressure when the condition is unrecognized or allowed to persist and shock and asphyxia from attempts at operative delivery. Zweifel, in 1909, suggested that intrauterine infection was an important cause of fetal death. He gives no figures to substantiate his opinion. Eastman, in discussing transverse presentation, reported an hour-glass contraction in 10 per cent of 93 full term cases, which constituted an important cause of fetal death. Chéron stated that the fetal mortality was due to interference with the placental circulation (4 cases of prolapsed cord) and interference of the after-coming head when version and extraction was done.

The percentages of fetal deaths in the various reported series are shown in Table I. Many of the collected cases appear in several reports, but it is quite evident that the fetal mortality is tremendous. Rudolph, in commenting upon his own fetal mortality, says that the fetal mortality should be less than 15 per cent. The only report that comes within Rudolph's *ideal* figure is that of Johnson's. In 105 cases that occurred in 7339 private patients, Johnson had a fetal mortality of 5 per cent. The title of his paper is significant, "Delay in Labor Caused by Mild Degrees of Bandl's Ring." In other words, he recognized the condition when there was a delay in labor and instituted treatment early. Thus it is seen that when constriction rings are not recognized early, there is a marked increase in fetal mortality. This is due in part to interference in fetal circulation, to amniotic sac infection incident to the long labor after the membranes have been ruptured, or to difficult operative delivery.

The present report is based upon 216 cases of constriction ring dystocia. Two hundred and two of these formed the basis of a report read at the meeting of the American Gynecological Society in June 1946. At that time I discussed the etiology and treatment of the condition. It is significant that in 2244 cases in which labor was induced by a Voorhees bag, constriction rings were found in 29 (1.25 per cent). In 5111 cases in which labor was induced by amniotomy there were 73 constriction rings or 1.46 per cent. In 6221 labors that were not induced

there were 100 (1.61 per cent) cases of constriction ring. In the whole series pituitrin was used in 748 cases and 21, or 2.8 per cent, developed constriction rings.

Since that report was written I have had fourteen additional cases or a total of 216 cases. There was one set of twins, so that I have 217 infants upon which to base my present report. Forty-two babies were lost, an uncorrected fetal mortality of 19.3 per cent. In the last 150 cases (counting the case of twins as two cases) there were 18 fetal deaths, a mortality of 12 per cent which comes well under the figure set by Rudolph. In contrast, in the first 67 cases there were 24 fetal deaths, a mortality of 35.8 per cent.

Table II shows the details of the cases in which there were fetal deaths. It will be noted that many of these cases showed other maternal complications that are associated with high fetal mortality. One mother, (23170) had diabetes that was difficult to control. She was sent into the hospital at the 37th week with the idea of delivering her by cesarean section. While waiting for the x-ray

TABLE I  
*Showing fetal mortality associated with constriction rings*

AUTHOR	NO. OF PERSONAL CASES	FETAL MORTALITY	COLLECTED CASES	FETAL MORTALITY
Cheron (1899)			67	44.9%
Smith (1882)	1	100%	32	75%
White (1916)	5	100%	19 (treated by abdominal section)	47%
Michael (1925)	4	50%	40	62%
Rudolph (1935)	21	24%	379	46%
Boulware (1936)	8	62%		
Pendleton (1937)	53	37.7%		
Johnson (1941)	105	5%		

report as to the condition of the baby, the mother went into labor. Labor was conducted under continuous caudal anesthesia. When the cervix was three-fourths dilated, she developed a constriction ring. There was no further progress in labor, and after two hours an attempt was made to deliver the baby. The ring did not relax with epinephrine. The patient was given deep ether anesthesia and a difficult forceps operation was done. The child died 1½ hours later of intracranial hemorrhage. This death was charged to constriction ring.

Two patients had eclampsia. One (5738) delivered a premature baby that lived 24 hours. The other (17705) delivered a stillborn baby. These deaths were thought to have been due to the eclampsia, as the ring readily relaxed and there was no difficulty with either delivery. Four mothers (1590, 5822, 6119, and 8080) had pre-eclampsia. All these deaths were charged to the toxemia.

On the other hand, the constriction rings complicated the delivery in two cases of placenta previa, (1030 and 8204), and these deaths were charged to the ring. One (8204) was a macerated fetus, and it was thought that the spastic condition had interfered with placental circulation. In the other case the presence of the ring may have delayed the delivery.



TABLE II

No.	Year	Age	Wt.	Ab.	Blood Pressure (and Antepartum Reading)	Placenta	Presentation	Delivery	Complication	Cause of Fetal Death
1030	1919	39	10	1	No A. P. Exam			Bag and Braxton Hicks Version	Placenta previa	Placenta previa
1506	1920	38	1	0	No A. P. Exam	Flat rachitic	R. O. A.	Version and extrac-tion		Enlarged thymus (autopsy)
1530	1920	17	0	0	150/90	normal	L. O. P.	Version and extrac-tion	Toxemia	Glioma in occipital region
1772	1920	40	6	1	No A. P. Exam	normal	R. O. P.	Version and extrac-tion		Antepartum death. Macerated fetus
2911	1922	40	13	0	normal	normal	R. O. P.	Craniotomy	Prolapsed pulseless cord	Macerated fetus
3070	1923	31	1	1	normal	normal	Breech	Bag and breech ex-traction		Intracranial hem-orrhage
3211	1921	26	0	0	No A. P. Exam	Flat rachitic	R. O. P.	Version and extrac-tion		Stillborn
3258	1925	28	3	0	No A. P. Exam		L. O. A.	Version and extrac-tion		Stillborn. Long labor
3388	1926	21	0	0	No A. P. Exam	Funnel	Breech	Breech extraction		Antepartum death. Macerated fetus.
4301	1926	25	0	0	115/80	normal	R. O. P.	Bag and mid-foreceps	Cord tightly about neck. Had to cut before delivery	Baby easily resus-citated. Died in 3 days
4738	1927	31	1	0	125/70	normal	L. O. A.	Mid-foreceps	Cord tightly about neck. Had to cut before delivery	Intracranial hem-orrhage. Tentorial tear

4742	1927	35	0	0	125/80	normal	L. O. P.	Bag and version extraction	Placenta previa	Difficult extraction
4983	1927	31	2	6	105/60	normal	R. O. A.	Bag and version		Lived a few days. No autopsy
5082	1927	38	2	2	110/100	funnel	L. O. A.	Mid-forceps	Overweight	Stillborn. Easy delivery. Total duration of labor 11 hours. Her 2 previous children were also still-born
5194	1927	32	3	0	170/120		Shoulder	Version and extraction. Abdomen entirely covered with scar from a burn	Heart disease	Ring did not relax
5238	1928	27	0	0	125/75	normal	L. O. P.	Bag and mid-forceps		Shoulders were hard to deliver
5738	1928	30	1	1	No antepartum exam		L. O. A.	Bag and Braxton-Hicks version	Eclampsia	Premature. Died in 4 hour
5822	1928	21	1	0	155/90	Justo-minor (Still-born)	R. O. P.	Bag Scanzoni forceps	Toxemia	Stillborn. Toxic death
6119	1929	28	0	0	155/97	funnel	L. O. A.	Bag and version	Toxemia	Macerated fetus. Toxemia
6639	1931	34	2	1	100/75	normal	R. O. A.	Bag and version		Baby died in 24 hours. Red cells 2,940,000

TABLE II (concluded)

NO.	YEAR	AGE	GH	WBS	BLOOD PRESSURE LAST ANTEPARTUM READING	PELVIS	PRESENTA- TION	DELIVERY	COMPLICATION	CAUSE OF FETAL DEATH
8080	1931	33	0	0	192 110		L. O. A.	Bag and version	Toxemia	Stillborn. Toxemia
8204	1931	33	1	0	140 90	normal	Breech	Extraction	Placenta previa	Macerated fetus
8300	1931	37	2	0	90 60	normal	Breech	Foro C. S.		Acephalic meningocele. Cleft palate
8310	1931	29	1	1	145 80	Justo-minor	Breech	Extraction craniotomy	Prolapsed cord	Macerated fetus
8391	1932	36	0	0	160 110	funnel	R. O. P.	Bag and version	Hydramnion	Intracranial hemorrhage
8614	1932	23	0	0	140 80	funnel	L. O. P.	Bag and version		Spoon-shaped fracture of left temporal bone
10599	1935	28	0	0	145 90	normal	L. O. P.	Version		Stillborn
10815	1935	41	3	1	130 80	Flat rachitic	R. O. P.	Amniotomy version		Tentorial tear
12370	1937	24	0	0	No antepartum exam		R. O. P.	Version	Prolapsed cord	Antepartum death and rigor mortis
12714	1937	41	2	1	No antepartum exam	normal	R. O. A.	Version after failed forceps on outside		Intrapartum death
14212	1938	28	0	0	No antepartum exam	normal	R. O. A.	Braxton-Hicks version		Spinabifida. Stillborn

14711	1939	31	0	0	No antepartum exam	funnel	R. O. P.	Version after waiting 12 hours for ring to relax	Stillborn
15965	1940	30	0	0	No antepartum exam	normal	Breech	Breech extraction	Tentorial tear
16665	1942	35	0	0	110/80	Flat	Brow	Version and extraction	Died in a few minutes
17276	1942	18	0	0	No antepartum exam		L. O. P.	Failed forceps. Version	Stillborn
17649	1942	19	0	0	No antepartum exam		L. O. P.	Mid-forceps	Stillborn
17705	1942	32	0	0	180/100	normal	R. O. P.	Bag and mid-forceps	Stillborn. Autopsy showed no cause of death. Toxemia
19255	1943	25	0	0	No antepartum exam	Justo-minor	R. O. P.	Craniotomy	Macerated fetus
19574	1943	26	0	0	124/80	normal	L. O. A.	Version and extraction	Stillborn
20375	1944	33	0	1	112/80	Justo-minor	L. O. A.	Amniotomy and mid-forceps	Stillborn. Amniotic sac infection
22187	1945	34	2	2	100/65	normal	Shoulder	Version and extraction	Hemorrhage into both suprenals
23170	1946	30	0	0	126/94	Justo-minor	L. O. P.	Mid-forceps	Premature. Intracranial hemorrhage

The three cases of prolapsed cord, (2914, 8310, 12370) were charged to constriction rings since this is a recognized complication of such a condition. Furthermore, the ring makes this complication particularly hazardous for the baby for it quickly cuts off the circulation by compression in the first place, and it delays the delivery of the baby in the second place. Case 1506 had a flat rachitic pelvis. Hospitalization was advised in the prenatal clinic, but was refused. After she had been in second stage labor for  $2\frac{1}{2}$  hours, fetal heart tones slowed to 80 per minute. Version and extraction was done under chloroform anesthesia. A constriction ring was felt to relax, but delivery was difficult on account of a flattened superior strait. The baby weighed  $7\frac{1}{2}$  pounds and was stillborn. Autopsy showed an enlarged thymus that extended over the upper half of the heart. There was no subdural hemorrhage nor any other cause of death discovered. This death was not thought to have been due to the constriction ring. Three babies (1590, 8300, 14212) had major deformities. One had a glioma in the occipital region associated with maldevelopment of the cranium. The second was an acephalic with meningocele and a cleft palate. The third had a spina bifida and was stillborn.

One baby (6639) died in 24 hours of anemia. The red cell count was 2,940,000. This was in 1931. It would be interesting to know this mother's Rh factor. She had had 2 previous children. Her third pregnancy terminated in an abortion at two months. She lived in West Virginia and all trace of her has been lost. This baby and the 3 deformed babies were not charged to constriction rings.

One baby (4394) died after an easy delivery with Kielland forceps when the ring relaxed. No autopsy was obtained. This death was thought to have been due to interference with the fetal circulation. Number 4983 was a similar case, but since this mother had aborted 6 times in 9 pregnancies, and since there was no autopsy to definitely fix the cause of the fetal death, it was thought that poor germ plasm was the more probable cause of this death.

There were 17 intrapartum deaths associated with difficult delivery, (3070, 3211, 3258, 4738, 4742, 5094, 5238, 8391, 8614, 10599, 10815, 12714, 14711, 15965, 17276, 17649, and 19574). Five were found to have intracranial hemorrhage. One of these was discussed under placenta previa. Another, (8614) had also a spoon-shaped fracture of the skull. All were charged to constriction rings. One other baby, not included in this group, because it was a postpartum death, also had an intracranial hemorrhage. This baby's death has already been discussed under diabetes mellitus.

One baby (22187) had hemorrhages in both suprarenal glands. It presented by the shoulder and was delivered by version and extraction without difficulty. Since hemorrhage into the suprarenals is a common occurrence in such deliveries, whether there be a constriction ring or not, this death was not attributed to the constriction ring.

The seven macerated fetuses (1772, 2914, 3388, 6119, 8204, 8310, and 19255) were all charged to constriction rings. It was thought that the uterine condition had caused an interference with fetal circulation. In case Number 6119 there was also present a placenta previa. The only other intrapartum death (5082) to



be considered is that of an overweight mother whose two previous babies were also stillborn. No autopsy was obtained. Since the delivery was easy, it was thought that some metabolic factor was more to blame than the constriction ring.

Number 16665 was a primipara with a flat pelvis. On two occasions in her pregnancy she was found to have a breech presentation. Each time an external version was done. When she went into labor she had a brow presentation. Progress was slow and when the cervix was 4 centimeters dilated the membranes were ruptured artificially. Progress was still slow, and when the cervix was about fully dilated examination with the hand within the uterus revealed a constriction ring. This readily relaxed with epinephrine, and an easy version was done. However, extraction was difficult, and the head had to be delivered with forceps. The heart continued to beat for 40 minutes, but the baby could not be made to breathe. There was no autopsy, but the spinal fluid obtained by cisternal puncture was bloody. This death was charged to constriction ring,

TABLE III

CAUSE OF DEATH	NUMBER OF CASES
	42
Other causes than Constriction Ring.....	13
Constriction Ring Dystocia.....	29
Difficult Delivery.....	20
Interference with fetal circulation (Prolapsed cord 3).....	8
Intrapartum infection.....	1

but the contracted pelvis probably had more to do with the dystocia than the ring.

One case exhibited definite signs of amniotic sac infection, elevated temperature, and cloudy membranes. The heart tones disappeared about the time the mother's temperature rose. This death was thought to have been due to the amniotic sac infection. There was no difficulty with the delivery.

#### DISCUSSION

The final allotment of the deaths to the various categories is shown in Table III. Difficult delivery is the most frequent cause of death. It is possible that some cases put into this category really belong in the next category. In either case some of these babies could have been saved had the constriction ring been recognized earlier. The question then arises, when a constriction ring is suspected shall we treat the mother expectantly in hopes that the ring will relax spontaneously and allow the labor to proceed normally or shall we subject the mother to the hazard of an intrauterine examination and an operative delivery in case a ring is discovered. Rudolph who has studied this question exhaustively, and who has had considerable experience, advocates the expectant plan. Undoubtedly the majority of rings are reversible. However, his fetal mortality is

18 per cent although he thinks it could be reduced to less than 15 per cent. On the other hand, Herman Johnson, whose idea in dealing with this condition is early diagnosis and prompt delivery, had a fetal mortality of only 5 per cent in 105 private cases. I have tried Rudolph's method in a number of cases but it has not served in my hands as well as it has in his. Cases 14711, 17649, 19255 and 20375 were treated in that manner.

If the macerated fetuses were due to interference with fetal circulation, it is difficult to see how the fetal deaths in this sub-group could be greatly reduced. It might be said that better prenatal care was the answer, but the 76 cases who had prenatal care had no better results than the 140 who did not have it. Some of the deaths from prolapsed cord could be prevented by closer supervision of the first stage. All three cases were brought into the hospital after pulsation had ceased. In regard to intrapartum infection, treatment with penicillin of cases of prolonged labor, especially when the membranes have ruptured early, is advised. However, this would cause no great reduction in fetal death rate if this series of cases is representative, as there was only one such case in 216 cases with constriction rings.

#### SUMMARY

An analysis of 42 deaths of a total of 217 infants born of 216 mothers who had constriction rings shows that 13 were due to other causes. Twenty-nine deaths were considered to have been due to the constriction ring. There was a difficult delivery in 20 cases. Eight deaths, including 3 cases of prolapsed cord, were thought to have been due to interference with fetal circulation. One fetal death was due to an amniotic sac infection. An analysis of the literature would seem to indicate that prompt recognition of the constriction ring followed by some type of operative delivery offers the best chance for the baby. My experience supports this point of view.

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## ALLERGY AND IMMUNITY

BELA SCHICK, M.D.

(*New York, N. Y.*)

All discussions on the subject of allergy should refer to the original work of Pirquet inasmuch as this scientist not only discovered allergy but coined the word. Study of the incubation time in disease was the foundation of his discovery. The usual explanation of the incubation period in "exotoxic" diseases like diphtheria is that it is concerned with the time required to produce a sufficient amount of primary toxin "exotoxin" to develop symptoms of the disease. It is interesting to note that the incubation period of this disease is relatively short and not fixed.

Another group of diseases, such as smallpox, measles, chickenpox, typhoid fever, and reaction to smallpox vaccination, has a relatively fixed incubation period of eight to fourteen days. This is so constant, in fact, that we can tell in advance when an infected individual will show the first manifestations of the disease. In view of these observations we assume that the symptoms of such diseases are due to the effect of "endotoxic" substances present within the body of the bacterial agent which is set free by bacteriolytic antibodies produced by the living organism. The explanation therefore of the incubation period in the aforementioned conditions is that the production of these antibodies requires from eight to fourteen days.

These two explanations are not applicable to the incubation period existing in serum sickness, which follows the injection of horse serum or other animal serum into the human organism. Here the incubation period is about eight to twelve days and is relatively fixed, being independent of the amount of serum injected. Serum as such is not toxic, it is a dead substance and does not multiply. There is no "endotoxin" to be set free.

Pirquet observed that when a child was reinjected with horse serum several weeks after the first injection, it showed immediate symptoms following the reinjection. There was no incubation period, hence the designation of an "immediate reaction." In further studies Pirquet and Schick showed that when the child was reinjected with horse serum four months or more after the first injection, there was no immediate, but an accelerated reaction, i.e., the child developed symptoms of serum sickness within four to six days—a decidedly shorter incubation period compared with the reaction after the first injection. It was realized that such reactions—immediate and accelerated—have diagnostic value. When an individual treated with horse serum gives an immediate or an accelerated reaction a diagnosis of a previous injection of serum may be made even without any actual knowledge of such an injection. This fact gave Pirquet the idea that skin tests may be applied for the diagnosis of a previous contact with the pathogenic substance or of a previous invasion by a germ or virus. Pirquet may therefore be regarded as the father of all skin testing.

Skin tests which have the most significant clinical application are the tuberculin test and those employed in asthma, hay fever, eczema, and many other skin rashes.

In a further study of the immediate and accelerated reactions following horse serum injections, Pirquet realized that the horse serum itself could not be responsible for the difference in incubation time, because the reinjected serum may have been taken from the same bottle as the initially injected serum. He concluded therefore that there must have been some change in the child to explain the difference in incubation time. The reactivity of the child must have been altered. For this altered reactivity of the individual a new term was needed and Pirquet coined the word "allergy."

In order to explain allergy or altered reactivity we formulated the following theory. Horse serum is a foreign protein which when introduced subcutaneously or intravenously (parenterally) acts as a foreign body, of which the organism must rid itself by destruction. This destruction is carried out in essentially the same manner as that of protein in the gastrointestinal tract, i.e., by digestion through ferments. A foreign protein is broken down to peptones, polypeptides and finally to amino acids. Peptone-like intermediary substances, i.e., histamine, are toxic. This toxic phase of digestion is normally quickly passed. The original protein and the amino acids are not toxic. The products belonging to the toxic phase are either not absorbed or they are detoxified by further digestion to amino acids within the intestinal tract or after absorption within the intestinal wall and liver, therefore not damaging the organism. However, while the gastrointestinal tract exists for the purpose of digestion and is prepared for it, the parenteral tissue is not. Ferment-like antibodies capable of digesting the foreign protein must be produced and this requires time. Pirquet called these antibodies "ergins." By interaction of the pathogenic substances of the horse serum with these antibodies (ergin) toxic substances similar to the substances of the toxic phase of digestion within the gastrointestinal tract are produced which are responsible for the symptoms of serum sickness. The toxic substances are not detoxified as foreign proteins during the enteral digestion, hence they exert their toxic effect on the cells of the organism. Pirquet felt the need for a new term for the toxic products created by the interaction of foreign protein with their antibodies, in order to differentiate them from the exo- and endotoxin. He therefore called these toxic substances "Apotoxin" signifying a toxic substance derived from an originally non-toxic substance.

The term "Apotoxin" has not been accepted in the literature and is therefore not used by Allergists. It is also never mentioned in the American literature except by Pirquet and Schick. I would therefore suggest in its place the designation of "Proteictoxin."<sup>1</sup>

Proteictoxin may therefore be considered as a toxic substance derived from (a) any protein (animal, human, plant, bacterial, virus) by interaction with its specific antibody; and (b) from chemical substances (drugs, lipids, carbohy-

<sup>1</sup> The word "protein" was used, but not in connection with toxin, by Coulson, E. J., Spies, J. R., Janson, E. F., Stevens, H.: *J. Immunol.*, 52: 259, 1946.

drates of bacteria, etc.) which combine with animal or human proteins, converting these haptens to antigens or allergens.

To prove the presence of antibodies in human beings *in vitro* is not always easy. The so-called passive transfer is evidence of their presence *in vivo*. Precipitins, however, may be demonstrated in human serum, three to four weeks after injection of horse serum. Precipitins for horse serum are readily produced and demonstrated in rabbits.

These antibodies once produced, do not disappear from the circulation immediately, but only very gradually and can be found even three to four months after the first injection. After the antibodies have entirely disappeared the reactivity of the organism is still altered. The initial injection of horse serum has evidently produced a permanent effect on the cells of the system. We assume that the latter "remember" how to handle the foreign protein, for on reinjection of the serum, antibodies reappear more rapidly than after the initial injection. As long as antibodies are present the reinjected serum will come in contact with them immediately. The toxic substances responsible for serum sickness are thus produced immediately and the so-called "immediate reaction" follows. No incubation time is necessary. When antibodies are no longer present the cells "remember" how to reproduce them more rapidly and the "accelerated reaction" takes place.

It may therefore be stated that in the light of this theory the original incubation time is necessary for the production of antibodies (ergins). The immediate reaction on reinjection of the pathogenic substance is due to the presence of these antibodies (ergins), the accelerated reaction is due to the ability of the cells to manufacture antibodies (ergins) more rapidly than at the first injection.

This theory can readily be applied in explaining the pathogenesis of many infectious diseases and the immunity which follows. Pirquet applied it in his study of the pathogenesis of smallpox, smallpox vaccination, measles, typhoid fever, etc.

The first vaccination is succeeded by a definite and regular incubation period. In performing a smallpox vaccination, the virus is implanted into the intracutaneous and subcutaneous tissues. During the first forty-eight hours nothing is seen except a traumatic reaction. On the third day a little papule appears, which grows daily, becoming vesiculated in the center. The enlarged vesicle assumes a silvery color, and pushes a small red area of inflammation forward. When vaccination is made with the boring instrument designed by Pirquet, the diameter of this reaction increases in arithmetical progression, resembling the growth of a bacterial culture in a petri dish. The attenuated smallpox virus multiplies, apparently irritating the local tissues. This irritation is visible in the inflammatory ring reaction around the central vesicle. Between the ninth and eleventh day, a large inflammatory reaction suddenly appears around the vesiculated center, and twenty-four to forty-eight hours later the growth at the center stops. The center dries up and becomes encrusted, while the large infiltrative redness around it fades slowly. The appearance of a large inflammatory area indicates the presence of antibodies in the circulation. They are able



to inhibit the growth of the virus culture at the center, kill the virus and liberate toxic substances. The existence of such antibodies can be proven in animals and human beings. If the serum is now mixed with the virus, the latter is found to be without visible effect.

If successive vaccinations are made daily during the incubation time of the first vaccination, each new vaccination develops in the same way. When the first vaccination manifests a large inflammatory area, similar reactions occur at the other vaccination sites. Further growth is stopped simultaneously with the reaction at the site of the first vaccination. The closer to the ninth day the successive vaccinations are made, the smaller will be the size of the vesiculated center at the time of appearance of the inflammatory area around it. The last vaccination does not develop at all. Under the influence of antibodies the smallpox virus is inactivated or destroyed. The individual is now clinically immune to revaccination and to smallpox. If vaccination is repeated several weeks later, the reaction will consist of a relatively small, rapidly appearing and rapidly disappearing papule and redness. The immediate reaction is explained on the assumption that antibodies are still present which are capable of inhibiting further multiplication and invasion of the smallpox virus. As in serum sickness, revaccination several years after the first vaccination does not elicit an immediate reaction, but an accelerated reaction. The papule develops on the third day, but grows only to the fourth or fifth day, when the large inflammatory reaction appears. Further growth of the culture of the virus in the skin is inhibited at this time. The whole reaction will be much smaller and will disappear in twenty-four to forty-eight hours. This accelerated reaction based on a more rapid reproduction of antibodies brings about sufficient immunity against the attenuated and fully potent smallpox virus.

In the reaction to revaccination we have a classical picture of allergy based either on the presence of antibodies leading to an immediate reaction or on the more rapid formation of antibodies, inducing an accelerated reaction. Both kinds of reactivity guarantee clinical immunity to smallpox. Similarly many other acute infectious diseases like measles and typhoid fever develop a state of allergy which protects the individual against a repetition of the new infection. Allergy is therefore the basis of acquired immunity. The quicker the antibodies can go into action the more complete is the immunity.

Many chronic diseases like tuberculosis, lues, etc. follow essentially the same pattern. Symptoms do not begin before the appearance of antibodies, which set free endotoxins or produce proteotoxins. Allergy is thus established. In these chronic conditions however the antibodies need a much longer time to arrest the disease completely. Indeed in most cases the disease is never completely cured, but only a compromise with the virus or bacillus is achieved. In tuberculosis, fibrosis and calcification may arrest the disease clinically; but in the center of the calcified lymph nodes living tubercle bacilli may still be found. In lues other factors lead to latency of the spirochete without visible symptoms of disease. In leprosy, too, we have a disease where allergy develops. But here, allergy is never able to arrest the disease without specific therapy and

the disease progresses until death intervenes. Allergic features manifest themselves in rheumatism; but here the exciting factor is not definitely known. Some believe that the streptococcus is the causative agent, others that the streptococcus is merely a complicating factor. Thus the clinical manifestations may be the result of an allergic reaction to the streptococcus to an unknown virus or to a combination of both.

Some investigators regard scarlet fever as the effect of an allergic reaction to a specific streptococcus. I attributed the initial symptoms of this disease to the action of a primary toxin derived either from a specific streptococcus or from an unknown virus which regularly combines with the streptococcus, whereas the nephritis, lymphadenitis and other complications were regarded by me as due to allergy. The peculiar crowding of these complications between the nineteenth and twenty-first day, the suddenness with which the symptoms appear, closely resemble the immediate reaction following reinjection of a pathogenic substance. On the basis of such a theory, the post scarlatinal complications are due to allergy of the individual organs. For example as a result of the first invasion of the scarlet fever toxin the kidney becomes particularly allergic. Antibodies which are produced in the following 2-3 weeks may interact with antigens arising from flare ups of the pathogenic germ and produce symptoms of nephritis. The other organs may also be capable of reacting in a similar way having been made allergic during the primary phase of the disease.

In addition to a change in incubation time due to allergy Pirquet found that there may also be a change in quality or in quantity of reaction.

A change in quality is seen for example in serum sickness where, instead of an urticarial eruption, we may have a morbilliform or a rubeolar rash. The change in quantity of reaction is usually in the direction of a diminution of intensity, as in revaccination.

In the case of serum sickness, however, it is peculiar that very frequently we see not a diminution but an increase in intensity of reaction. Such intensified reactions are called hyperergic reactions and can be partly explained (especially when the reinjection is done by the intravenous route), by the fact that a large amount of the serum comes in immediate contact with the antibodies. It must, however, be admitted that intensified or hyperergic reactions cannot be entirely explained on the basis of increased dosage of the foreign protein. The increased intensity of symptoms is due to a basic hypersensitiveness of the individual to the pathogenic substance, produced by previous introduction of that substance. This hypersensitiveness to reinjection of horse serum has been especially studied in experimental animals. It was found that the guinea-pig tolerated the first injection of serum without any conspicuous symptoms; but intravenous reinjection of the serum brought about sudden death to the animal. Theobald Smith in this country observed this sudden death in guinea-pigs. Richet was the first to observe such sudden death in dogs, after reinjection of the poison of actinea. He thought that the first injection of the poison led to an inactivation or a suppression of protective substances against that poison. For this reason he introduced the term "anaphylaxis," which means "without protection."

The damaging effect of hyperergic (anaphylactic) reaction does not occur in the usual course of the acute infectious diseases. In these diseases the allergic state, through the presence of antibodies or their more rapid formation stops the further multiplication of the invading germs and thus prevents greater damage and is a decided advantage. The quicker the defense mechanism can be brought into action, the less time the virus or bacterium has to multiply and therefore only a small amount of toxic substance is produced or liberated—an amount insufficient to produce clinical symptoms and certainly insufficient to elicit hyperergic (anaphylactic) reactions, even in a case where the individual is hyperergic. Immunity is thus established.

The damaging effect of a hyperergic reaction may occur in the course of a chronic infectious disease like tuberculosis where the antibodies are not able to stop the multiplication of the invading organisms completely. Massive invasion of the circulation by tubercle bacilli from a tuberculous focus within the body or massive superinfection from without may produce a violent inflammatory reaction in a hypersensitive individual infected with tuberculosis.

The combination of hypersensitiveness and exposure to increased amounts of the infectious agent does not occur frequently enough to outweigh the marked advantage of the allergic defense mechanism. We may say that in the human being certain types of allergic reactivity guarantee clinical immunity. The hyperergic reactivity in these instances does not come to the fore and does not interfere with the beneficial effect of the allergic state.

The theory propounded by Pirquet and Schick, that allergic and hyperergic reactions are due to an interaction between antigen and antibodies is still valid, and many experimental facts (passive transfer, reversed serum sickness, etc.) support it.

There are, of course, many other concepts concerning the pathogenesis of allergic and anaphylactic (hyperergic) reactions. One of those advocated by certain French investigators (Villaret, Vallery-Radot and others) is to the effect that the symptoms of allergy may depend upon an excess of acetylcholine or upon some disturbance in its normal breakdown by the choline esterase. Urbach contends that acetylcholine and similar substances are formed as the end results and not immediately by the interaction of antigen-antibody. Endotoxins and proteictoxin may likewise liberate or produce these substances from the cells. Histamine may be one of the proteictoxins arising during the antigen-antibody interaction but not the only one. However, histamine may be also liberated from the cells through the irritating effect of other substances, produced by the antigen-antibody interaction.

Doerr is the outstanding champion of the physical theory as the basis of the anaphylactic shock. He assumes that the antigens and antibodies, substances of high molecular weight, react on the cell membrane but do not penetrate it. As a consequence physico-chemical changes are instituted, which act as irritant to the cells. According to Bronfenrenner the interaction between antigen and antibody serves to disturb the delicate adjustment of the colloidal conditions existing in the serum as well as at the surface of the tissue cells. Widal looks

upon anaphylactic shock as representing a disturbance of the colloidal balance. He and his school designate the changes of the colloids in the blood observed during attacks as "hemoclastic crisis" and those in the tissues as colloidoclasia. Lumiere on the contrary explains the nature of anaphylactic phenomena on the basis of invisible flocculation occurring in the blood stream of allergic individuals as the result of the encounter between antigen and serum antibody. In support of his views he cites the fact that *in vitro* flocculation follows the mixture of the antigen with the serum of allergic individuals.

These various theories may have an important bearing in explaining the anaphylactic shock, but cannot be applied as an explanation for all allergic phenomena.

The guinea-pig differs from the human being in that it consistently presents the disadvantageous phases of allergy—hyperergy. Hyperergic reactions to horse serum and other foreign proteins are so impressive that other features of allergy are easily overlooked. Confusion in the relation between allergy and immunity has its roots in the fact that the serologist has studied and still studies only hyperergic or anaphylactic reactions to horse serum in the guinea pig and then identifies these with allergy in its entirety. This confusion is further increased because similar anaphylactic reactions are likewise elicited in hypersensitive human beings—in asthmatic patients, or patients with eczema, without previous injection of serum.

Moreover, study of the asthma syndrome has shown that it is frequently induced by the inhalation of different protein substances such as pollen, house dust, animal emanations, moulds or food. This manifestation of hypersensitivity is not combined with immunity, but relief may be accomplished either by removing the offending agents, or by de-sensitizing the victim by repeated injections of the offending substances in increasing amounts. Here as in serum sickness we are not dealing with a living, multiplying, invading agent such as is present in infectious diseases and consequently the existing allergy does not confer immunity.

I am impressed by the observation that the majority of substances responsible for asthma and allied hyperergic conditions are protein substances present in germ-cells and their surroundings. Such proteins are not completely differentiated but are so constituted that they are ready for conversion to the more specifically differentiated proteins of the organs of a plant or animal. Pollen, eggwhite, wheat-germs and other seeds stand in the frontline of allergenic substances. Milk and blood serum come next in line. Oysters and other lower organisms, i.e., bacterias, moulds and viruses, with less differentiated proteins are frequent offenders. The fact that fish protein plays a great role in hyperergic diseases may be explained on the assumption that their protein is less differentiated than the organ protein of human beings. Even human beings go through a fishstage during embryonal life. In following up this idea in association with Rose Spiegel we could establish the fact that many individuals who are clinically sensitive to eggwhite can eat chicken without showing allergic symptoms. This points to some difference in the antigenic character of the



protein of the chicken muscle as compared with the protein of eggwhite, although by skin tests they may often react both to egg and chicken protein. These less-differentiated proteins seem to be more capable of producing antibodies leading to hyperergic reactions.

#### THE TUBERCULIN REACTION

The tuberculin reactions (Pirquet, Mantoux, Moro, Vollmer) are all allergic reactions. The same theory applies here as in serum sickness, namely that the interaction between tuberculin and specific antibodies produces the toxic substances responsible for the reaction. Tuberculin itself is not toxic except for the individual infected with tuberculosis. Pirquet's great contribution was to demonstrate that a positive tuberculin reaction is proof of the existence of a tuberculous focus in the body. There is one important difference between the pathogenesis of serum sickness and the tuberculin reaction. It is impossible to produce a positive tuberculin reaction by repeated injections of tuberculin. Inflammatory reactions at the site of reinjection in an individual free from tubercular infection are most likely not specific but represent "pseudo reactions" to various substances in the solution. Living or dead tubercle bacilli must first be injected in order to produce sensitiveness to tuberculin. In human pathology a tuberculous focus is necessary to elicit and sustain sensitiveness to tuberculin. Lipid substances and carbohydrates in tuberculin and tubercle bacillus may act as haptens, becoming antigens by combining with protein substances of the organism. We are not referring here to the production of a positive reaction by a mixture of pig serum or vaccine with tuberculin or by using nucleoprotein fractions of tuberculin (Seibert).

The guinea pig infected with tuberculosis becomes allergic to the tubercle bacillus and its products. Koch, antedating Pirquet, demonstrated that such a guinea pig shows more resistance to artificial reinfection in the skin. The inflammatory reaction at the site of the superinfection develops earlier and is resolved quickly without necrosis. According to Pirquet tubercle bacilli introduced into such an allergic guinea pig are more quickly arrested in their growth and a smaller amount of toxin is liberated. The guinea pig can however be killed by reinjection of a greater amount of tubercle bacilli or by larger amount of tuberculin. The allergic reaction of the guinea pig is the expression of the presence of antibodies.

On the basis of this mechanism a certain resistance against superinfection with tubercle bacilli exists. The same may hold for the human being. Infection with tuberculosis leads to a greater resistance against re- or superinfection to a limited extent. Such invasion may be quickly arrested on account of the existing allergy. Massive re- or superinfection, however, can be dangerous for the dissolution of a great number of tubercle bacilli may produce a violent or even fatal reaction, if the individual is highly sensitive to tuberculin and other substances of the tubercle bacillus. For this reason we separate children with closed forms of tuberculosis from those with open lesions, knowing that massive and repeated superinfection may occur. The greater resistance of a child



infected with tuberculosis against small and limited superinfections is based on allergy. We therefore assume that the first infection with tuberculosis is rather an asset for the child. We teach that the type of tuberculosis which occurs about the time of puberty or later in the adult develops only in an individual previously infected with tuberculosis (reinfection type of tuberculosis). If an individual is infected with tuberculosis for the first time at puberty or as an adult, that individual develops the so-called "childhood type" or in other words "first infection type" of tuberculosis. The allergy established by the primary infection is necessary for the reinfection type of the disease. Why puberty lowers resistance and permits the reinfection type to develop is not quite clear. When superinfection leads to active disease in adult life we assume that the individual's resistance has been lowered by some debilitating disease by unhygienic conditions—overcrowding, overwork, poor nutrition, etc. Only a small percentage of persons infected in childhood develops active tuberculosis later in life. This conclusion is drawn from the fact that although 94 per cent of the children of fourteen years of age admitted to the children's ward in Vienna had a positive tuberculin reaction, without signs of active disease and practically everybody of the social stratum of a hospital patient had a positive tuberculin test at the age of twenty, relatively few developed active tuberculosis in later life. Only the war and postwar starvation brought about a rapid increase of active tuberculosis.

Myers and Stuart had the opportunity to study children at the Lymanhurst School and to follow them for many years. They found that children who had a calcified primary complex at six or seven years of age and were in perfect health, came down with a rapidly progressing tuberculosis at the time of puberty. They, therefore questioned the concept dealing with the beneficial effect of a primary complex on the tuberculosis of later life. They pointed out that the children who had been infected with tuberculosis in early life were worse off than those whose primary complex developed at the time of puberty or later. In the latter children the primary complex developed slowly and these children were not as violently affected as were those of the same age who suffered superinfection. As a consequence of this reasoning, Myers and Stuart denied the beneficial effect of allergy and also denied that allergy has anything to do with immunity.

Their ideas were supported by the experiments performed by Rich and Pagel, in which they showed that allergic animals produced more intense reactions at the site of reinjection which went to necrosis. Rich further showed that he could abolish an allergic reaction in the skin by repeated injections of tuberculin but the increased resistance of such animals against reinfection, was still present. On the basis of having separated skin reactivity and resistance to reinfection, Rich claimed to have separated allergy from immunity. I think that these experiments show only that the hyperergic reaction of the skin and other tissues to tuberculin can be rendered less intense or even invisible. The resistance produced by the immediate and the accelerated interaction between the invading tubercle bacillus and antibodies is still present. Myers and Rich have separated the anaphylactic part of reactivity from allergy. Even Rich has to admit that

his idea of separation of immunity from allergy is based on the fact that he has dropped the original meaning of allergy defined by Pirquet, as an altered reactivity. He admits, however, that allergy taken in the original sense of Pirquet, covers not only hyperergic reactions, but also immunity.

Credit should be given to Myers and Rich for proving that skin hypersensitiveness and hyperergic reactivity as a whole may be a disadvantage to the tuberculous individual, as this hyperergic reaction exists in all organs and particularly in the lungs. Therefore, an attempt to diminish the hyperergic reaction by tuberculin treatment is justified. Desensitization with tuberculin in suitable cases should be revived. But we must realize that desensitization with tuberculin resulting in negative skin tests does not mean that allergy leading to better resistance has been destroyed.

Clarification of our ideas concerning hyperergic reactions in their relation to allergy as a whole is very important. It would be a step backward if we were to accept the theory that allergy has nothing to do with immunity. It is correct to say that the anaphylactic reaction is only one aspect of allergy—an unpleasant and damaging phase, while immunity represents the beneficial effect of allergy.

As a sequence to this concept we will find that despite a common basis in pathogenesis the bacterial infections (virus included) may be distinguished from the outspoken proteictoxic disease such as serum sickness, asthma, eczema and related conditions, by the fact that the former clearly demonstrate the beneficial part of allergy because exotoxic and endotoxic effects leading to immunity dominate the clinical picture while the proteictoxic effects are more or less in the background.

However, in the outspoken proteictoxic diseases where no exo- or endotoxins are present no immunity exists or develops. The hyperergic reactions prevail and impress the observer by the intensity of their manifestations.

Between these two groups stand tuberculosis and similar chronic diseases such as rheumatism and leprosy. These conditions are characterized by the presence of endotoxins, lipids, carbohydrates and protein substances, which act in a specific manner. Tuberculin, which is the most important substance produced by the tubercle bacillus is not toxic as such but behaves like serum and becomes toxic by interaction with antibodies. The danger of hyperergic reactions inherent in tuberculosis is counteracted, as previously indicated, by the beneficial phase of allergy. The same holds true for other diseases similar to tuberculosis.

When Pirquet coined the term allergy he did so in order to differentiate the immunity in exotoxic diseases (diphtheria, tetanus) based on the presence of antitoxic antibodies from the immunity established through immediate and accelerated reactions in endotoxic and proteictoxic infectious diseases. Pirquet stressed the fact that exotoxin is neutralized by antitoxin so that no reaction and no clinical symptoms whatsoever appear. Endotoxic and proteictoxic diseases may lead to "clinical" immunity by the development of immediate and accelerated reactions which diminish the amount of toxic substances set free under favorable conditions. Symptoms may be latent but evidence of sensitization may be obtained by cutaneous and intracutaneous testing. The presence of antibodies or

their rapid reappearance reduces the amount of reactive toxic substances in these diseases to a minimum.

Allergy develops wherever antibodies are produced no matter whether antibodies are antitoxic, antibacterial, antibiotic, or antiprotein in nature. We may presuppose that the mechanism of production of antibodies is essentially the same, whether we deal with antitoxic, antibacterial, antibiotic, or antiprotein antibodies. Thus allergy must exist in exotoxic diseases too. The production of antitoxic antibodies also needs an incubation time. Antitoxic antibodies appear one or two weeks after the first invasion by pathogenic organisms such as diphtheria bacilli, or even later. The antitoxic antibodies prevent further damage by exotoxin and terminate the progress of the disease. Antitoxic substances produced by the patient himself are present in the blood stream for some time. Should the infecting germ (e.g., the diphtheria bacillus) reenter the organism, the exotoxin of the bacillus is immediately neutralized by the antitoxin present in the serum and no clinical symptom will develop. This neutralization corresponds to the immediate interaction between endotoxin and protein substances with their respective antibodies in the "endotoxic and proteictoxic diseases." This antitoxic immunity is a humoral immunity based upon circulating antitoxic antibodies. After a certain time these antibodies may also disappear so that the humoral immunity is lost. But just as in the infectious diseases (measles, etc.) due to endotoxin and proteictoxin, antitoxic antibodies reappear quicker at the second or repeated invasion than after the first invasion. The tissue cells are capable of reproducing the antitoxic antibodies more rapidly (and eventually in greater amount) than after the first invasion. Hence in exotoxic diseases we also find an "accelerated" interaction between exotoxin and antitoxin within the organism, neutralizing the effect of the toxin more quickly than the first time. This represents a cellular immunity.

Thus, as far as the mechanism of antibody production is concerned no difference exists in the various diseases enumerated. The difference exists only in the result of the interaction between antigen and antibody. In exotoxic diseases this is characterized by the neutralization of the exotoxin, whereas in endotoxic and proteictoxic diseases by the counteraction of toxic substances in varying amounts leading either to negligible and therefore invisible symptoms or to manifestation of the specific disease.<sup>2</sup>

In 1910 I published a paper concerning immunity in diphtheria dealing with the study of a girl of 13 $\frac{3}{4}$  years who came down with diphtheria for the fourth time and had no antitoxin in her serum on the second day of her disease.

The first attack occurred in her ninth year. It was a severe pharyngo-laryngeal-diphtheria which subsided under treatment with serum and intubation within four weeks. The second attack—a mild localized diphtheria—occurred a year later. The patient was discharged after three weeks. At eleven years of age the patient again had a mild attack of diphtheria and remained in the hospital only ten days. In February, 1910 the girl was readmitted with a typical mild form of

<sup>2</sup> It is understood that all antibodies originate from the cells of the organism and appear in the serum so to speak as an overflow. Thus the humoral immunity is really also a cellular immunity.

diphtheria. She had membranes on both tonsils. The culture was positive. The brother of the patient was also admitted to the hospital because of diphtheria. As indicated, the patient herself had no antitoxin in her serum and was not treated with antitoxin serum, in order to study the appearance of antitoxin. The interval between the third and fourth attack was  $2\frac{3}{4}$  years. In spite of the repeated attacks of diphtheria the child had no antitoxin in her serum. However, these attacks showed varying intensity. The second attack was less marked than the first and the third and the fourth attacks were very mild. Therefore, the previous attack had an influence upon the immunity of the child. This was clearly shown by examination of the serum. On the sixth day after the onset of her symptoms the patient had an antitoxin content of 0.035 A.U. in 1 cc. and on the thirteenth day, 0.8 A.U. in 1 cc. of serum.

This individual was therefore able to produce antitoxin rapidly and in large amounts. The mildness of the third and fourth attack may be explained by the accelerated reproduction of antitoxic antibodies. The disease was not only mild but was terminated quickly.

The accelerated production of antitoxic antibodies characterizing the cellular form of immunity is the basis of the now practised "Stimulating or Booster Dose" in diphtheria and tetanus immunization. They transform the cellular immunity (potential in nature) into a humoral immunity, bringing back into circulation the antitoxic antibodies. These concepts have been presented in 1910 at a pediatric meeting in Koenigsberg and again in 1932 in a contribution to the Libman Anniversary Volume. They may be also found in my articles on "Diphtheria" in Pfaundler-Schlossmann Handbook on diseases of children (1932) and in Brenne-mann's Handbook of pediatrics, Vol. 2, chapter 4, page 8.

In order to avoid confusion, the role of proteictoxic substances in the symptomatology of bacterial and virus infections and that of exo- and endotoxin needs some classification. The characteristic symptoms of all infectious diseases are to a great extent determined by exotoxins and the liberated endotoxin, both of which are primarily toxic. Besides these specific exo- and endotoxins other protein containing substances exist.<sup>3</sup> The latter are handled by the body in a way similar to that of foreign serum and converted into proteictoxins by specific antibodies. They too may produce inflammatory and other reactions in the organism. Symptoms due to such proteictoxins are part of the classical symptoms of the disease, but are as a rule not conspicuous except in tuberculosis where the tuberculin effect is an outstanding factor in producing clinical manifestations. They are responsible for reactions which we can reproduce in the "pseudo- or para-reactions" by testing individuals with material which contains a protein element besides exo- or endotoxin. These protein substances are also specific inasmuch as they belong to the bacterium, but are, for instance in the case of diphtheria, not neutralized by antitoxin. Similar proteictoxins can also be found in endotoxic diseases and may likewise produce some additional symptoms. The antibodies mediating the development of proteictoxin may be produced simul-

<sup>3</sup> Such protein substances may be excreted or secreted by the germs or may be present in the body of the inciting germ (exoprotein and endoprotein).

taneously with the bacteriolytic, antitoxic and other antibodies. The stimulus for their production arises from the destruction of the infecting agents. That such antibodies exist in natural disease can be demonstrated by the fact that pseudoreactions to the diphtheria-toxin solutions (Schick-test) are frequently encountered in the course of diphtheria. Whereas the Schick test prior to the disease is positive without showing a pseudoreaction. Such pseudoreactions may be seen after the disease. Apparently the infection with the diphtheria bacillus leads not only to the production of neutralizing antitoxin but also to antibodies against protein substances of the diphtheria bacillus capable of creating proteictoxic substances. It is interesting to note that whereas the exotoxin of the diphtheria bacillus is easily destroyed by heat and neutralized by antitoxin, the substances convertible to proteictoxin are not affected by heat or antitoxin. Thus the pseudo- or parareaction can be differentiated from the true exotoxic reaction.

It will be now clear that exo- and endotoxic substances are primarily toxic and do not need to be converted into toxic products. Protein substances of the bacterium or substances attaching themselves to protein (haptens) are converted by their interaction with specific antibodies into a toxic proteictoxin. Such protein substances are present in allergens like foreign serum, food, inhalants and other irritating substances responsible for the symptoms of asthma, urticaria and the various forms of so-called allergic (hyperergic) diseases.

In the majority of cases the proteictoxic substances produce a wheal-reaction in the skin similar to that produced by histamin. But clinically different forms of reaction are seen in response to tuberculin and to tests in eczema, in contact dermatitis and in cutaneous manifestation of drug allergy. They show macular, papular and erythematous lesions. These may be the result of different proteictoxins which may be responsible for the difference in clinical symptoms.

It must be born in mind that the simplification of the mechanism of allergic reactions has its limitation. Even if we accept that histamine may be one of the proteictoxins inducing inflammatory reactions like the pseudoreactions, characterized by maculopapulous eruptions, delayed reactions in hay-fever testing cannot be explained by claiming histamine as the exciting agent.

Davidson pointed out that in the different skin eruptions during serum sickness the urticaria is due to the Euglobulin fraction of the serum, the ringform to the albumin fraction and the morbilliform eruption to the pseudoglobulin fraction.

If horse serum contains many different protein fractions which produce different biological effects one may imagine how much more complex may be the reaction resulting from the actions of a bacterial agent whose secretions and excretions in addition to the somatic proteins form sources of sensitization. It is therefore wrong to explain all the manifestations of allergic reactions by a theory that one substance does everything.

I hope that this survey of allergy, anaphylaxis and immunity will be helpful in clarifying the confusion existing in this field. Many details have been left untouched and there is a great deal yet to be explained in the study of allergic disease.



## ENCAPSULATED FOREIGN BODY IN THE PERITONEAL CAVITY

LEO S. SCHWARTZ, M.D., F.A.C.S. AND PAUL PEDOWITZ, M.D.

(*Brooklyn, N. Y.*)

A foreign body such as a gauze pad left within the peritoneal cavity during an abdominal operation is not an uncommon accident. Such an accident constitutes a serious hazard to the patient and a nightmare to the surgeon.

Wilson, in 1884, collected 30 cases of retained sponges; Neugebauer of Warsaw, in 1900, published a large series of cases, one as early as 1859. In a review of 215 cases of retained sponges wherein the nature of the operation is stated, 134 or 62 per cent occur during gynecological and obstetrical procedures. An analysis of these 134 cases found that 37 were operations for ovarian neoplasms, 30 were hysterectomies, 28 for pelvic inflammatory disease, 18 for ectopic gestation, 12 were cesarean sections, 7 myomectomies and 2 for uterine suspension. Why these accidents occur more frequently in obstetrical and gynecological procedures is difficult to hypothecate.

Three types of reactions may occur in the peritoneal cavity when a gauze pad is retained therein: 1) Infection: This usually terminates in the formation of an abscess and most commonly occurs within six months after the operation. 2) Expulsion: The foreign body may be expelled from the peritoneal cavity by the path of least resistance as through the intestinal tract and rectum, vagina or bladder. 3) Aseptic inflammation and encapsulation: The longer the foreign body is retained in the peritoneal cavity, the greater is the possibility of its becoming encapsulated.

In the statistics compiled by Crossen and Crossen, 1 out of 48 cases showed aseptic encapsulation in 4 to 6 months after operation; 10 out of 30 in 2 to 3 years; 4 out of 7 in 4 to 5 years, and 5 out of 14 after 5 years. The longest period of time an encapsulated sponge has been retained was 25 years after an abdominal operation. To date, only 20 cases of encapsulated sponges have been reported in the literature.

The mechanism of aseptic encapsulation comes into play when there is neither an infective process within the peritoneal cavity, nor any process attracted to the foreign body from the blood stream or contiguous organs. The sponge is usually within some silent area in the abdomen so that the protective and reparative forces may work undisturbed.

Bunger was the first to demonstrate the mechanism of aseptic encapsulation by animal experimentation. Within sixteen to twenty-four hours after a sponge was inserted into the peritoneal cavity, he found it to be completely surrounded by a grayish-white capsule that was fixed to the peritoneum. Microscopically, the capsule consisted of several layers of fibrin, the latter plus round cells were present in the meshwork of the sponge. The continuity of the peritoneal epithelium was broken in the area of the sponge and there was early evidence of fibroblastic activity in the fibrin network. Within two days, a rich growth of

cells was seen on the surface of the foreign body and a cellular exudate penetrated deeper into its core. By the third day, the zone of cellular exudate completely penetrated the core of the foreign body and the periphery was replaced by granulation tissue. This process continued until the seventh day, when a complete capsule of granulation tissue was formed. (We believe that in our case, this mechanism was aided by a blood clot that surrounded the sponge.) During the second and third year, the mass tends to be intimately adherent to the adjacent structures, whereas in the fourth and fifth years, the mass as a



FIG. 1. Note calcific area within tumor mass

rule lies freely within the peritoneal cavity except for an occasional fine adhesion. If the sponge is removed within five years (of the operation), it shows very little change in structure or texture. After five years have elapsed, one or more of three changes may be observed, namely: calcification, partial absorption of sponge fibers, and disintegration and diffusion of the sponge fibers in various directions. In our case, the sponge showed some evidence of calcification.

#### CASE REPORT

*History.* The patient, a married white female, aged 32 was admitted to the Jewish Hospital of Brooklyn, on December 25, 1944 with the following history.

On June 6, 1936, a low flap cesarean section was performed for a cephalo-pelvic disproportion. The post-operative course was uneventful until the sixth day when the patient's temperature became elevated. A diagnosis of thrombo-phlebitis of the left lower extremity

was made at this time and conservative measures instituted. The patient recovered and was discharged on the nineteenth day after the operation.

† In June 1942 she again conceived, and in the latter part of September consulted the senior author because of a mass in the pelvis. Examination at this time revealed the

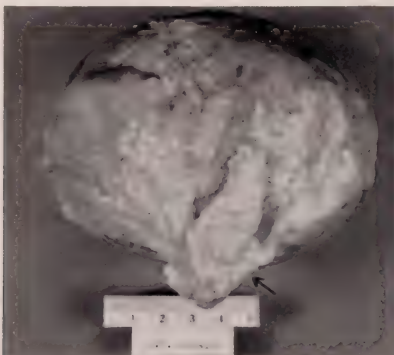


FIG. 2. Note resected tags of omentum at upper pole of cyst

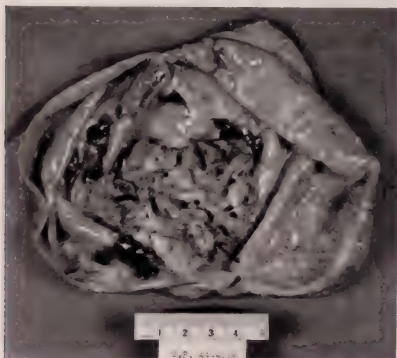


FIG. 3. Note hair-like material within cyst cavity

fundus below the umbilicus, fetal movements were audible, and there was a smooth moveable cystic mass in the right upper quadrant of the abdomen. A diagnosis of ovarian cyst complicating pregnancy was made. As the patient had no symptoms referable to the mass, she was advised to return to her obstetrician and have the mass removed at the time of the cesarean section. On February 23, 1943 a cesarean section and sterilization were performed. In September 1944, the patient again consulted the senior author because of the persistence of the mass in the abdomen. Examination revealed a smooth, freely move-

able mass the size of a fetal head in the left iliac fossa. An operative procedure for the removal of the cyst was advised.

*Examination.* There was a firm, healed scar in the median suprapubic area of the abdomen. A round cystic mass, the size of a fetal head, could be displaced into the pelvis, the epigastrium and either flank. On pelvic examination the uterus was found to be anterior, normal in size and freely moveable; the adnexae were not palpable. A flat plate of the abdomen revealed the mass to have some peculiar unidentifiable calcified areas (fig. 1).



FIG. 4. 4×4 inch gauze

*Operation.* On December 26, 1944 a laparotomy was performed. An opaque cystic mass was found in the mid-abdomen with the free border of the omentum attached to its superior aspect. Both ovaries were normal and the tubes presented evidence of previous ligation. The omentum was then resected at its point of attachment and the mass removed. The post-operative course was uneventful and the patient was discharged on the 11th day.

*Description of the specimen. Gross.* The specimen consisted of a mass measuring 11.6 x 9.2 x 8.2 cm. The external surface was smooth, pink and gray, and glistening. Tags of adipose tissue were firmly adherent to the external surface and separated with difficulty. The consistency of the mass was somewhat doughy. On section, fluid and a mustard-colored grumous substance admixed with hair-like material were seen; the cyst wall was

ragged, grayish-pink in color with scattered purple patches, and completely covered with the grumous material. On closer examination, the hair-like material was found to be a 4 x 4 inch piece of gauze (figs. 2, 3 and 4).

*Microscopic observations.* No definite lining to the cyst was demonstrated. The wall was composed of dense fibrous connective tissue infiltrated by mononuclear cells and

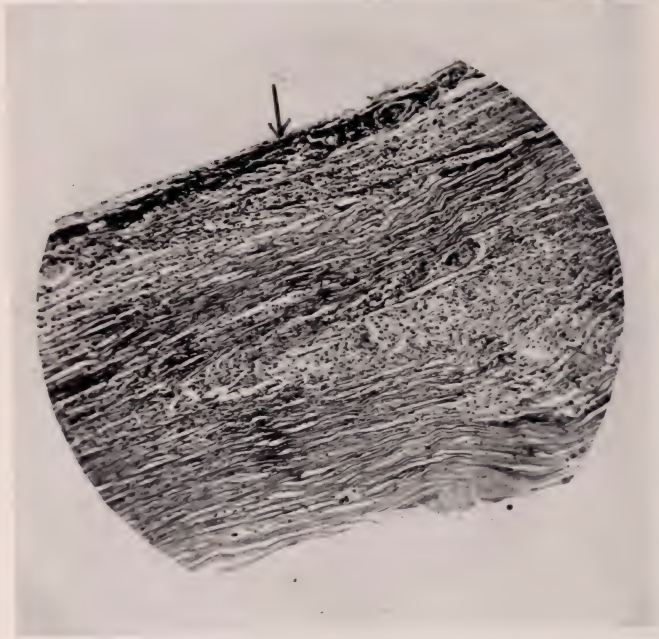


FIG. 5. Note absence of true cyst lining

scattered pigmented cells (this process was also seen in the attached lobules of adipose tissue); other sections showed areas of necrosis, old and recently extravasated blood, desquamated amorphous material, and bizarre configurations of boat-like clefts and needle-like spaces. The mass was infiltrated with small and large mononuclear cells, islands formed by large pleomorphic cells with a foamy cytoplasm and a small nucleus, and an occasional multinucleated giant cell of the foreign body type (fig. 5).

#### SUMMARY

1. A case of aseptic encapsulated sponge removed 8 years after the primary operation is reported.



2. Of all cases of retained sponges reported, 62 per cent have been found to follow obstetrical and gynecological procedures.

3. The mechanism of aseptic encapsulation and changes in the sponge are described.

#### CONCLUSIONS

1. Thorough exploration of the intra-abdominal cavity during a laparotomy should always be performed.

2. The use of  $4 \times 4$  inch gauze pads should be avoided when the peritoneum is open.

3. Only large laparotomy sponges should be employed while the peritoneal cavity is open.

4. Laparotomy sponges should be examined for extraneous material (such as unaccounted pieces of gauze and instruments) by the assisting nurse before use by the surgeon.

5. Careful and complete check of sponges used should be made before closing the peritoneal cavity.

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## CHEMOTHERAPY OF SUBACUTE ENTEROCOCCUS ENDOCARDITIS

JONAS H. SIROTA, M.D.; ISADORE E. GERBER, M.D. AND GEORGE BAEHR, M.D.

(New York, N. Y.)

*From the Medical Services of The Mount Sinai Hospital, New York*

With the advent of specific chemotherapeutic agents, the bacteriological differentiation between the enterococcus and the *Streptococcus viridans* group of bacteria recovered from the blood stream in cases of subacute bacterial endocarditis ceased to be of purely academic interest. The prognostic significance of this differentiation has now become of paramount therapeutic importance. Before the introduction of sulfonamide therapy in 1938, spontaneous cures were said to occur in only 1 to 3 per cent of all cases (1), regardless of the causative organism. Subsequently a recovery rate of from 7 to 10 per cent was reported in cases caused by *Streptococcus viridans* when treated with sulfonamides either with or without hyperthermia (2 and 3).

During the five year period preceding the introduction of penicillin (1938 to 1943) we used oral sulfonamide therapy in 81 patients with subacute bacterial endocarditis, with 8 cures, a recovery rate of almost 10 per cent. Of the 8 patients who recovered, 3 had congenital heart disease with *Streptococcus viridans* as the infecting agent, and two others had *Hemophilus influenzae* as the responsible organism. Three out of the 5 cases with congenital heart disease and *Streptococcus viridans* endocarditis and 2 out of 3 patients with *H. influenzae* infection of rheumatic heart valves recovered on oral sulfonamide therapy. If these exceptionally favorable cases are excluded, there were only 3 out of 73 patients with endocarditis due to *Streptococcus viridans* or related organisms who recovered on oral sulfonamides, a recovery rate of 4.1 per cent.

In 1943 we employed massive intravenous sulfonamide therapy in a series of 16 cases with recovery in 6, a cure rate of 37.5 per cent (27). There was one treatment fatality. When penicillin became available, a recovery rate of 60 to 77 per cent or more was uniformly achieved (4-9). In spite of these brilliant results with the penicillin treatment of subacute bacterial endocarditis due to *Streptococcus viridans*, and other organisms, the enterococcus proved, as a rule, to be resistant both to sulfonamides and to penicillin. The discovery of streptomycin gave promise of adding an effective agent in the treatment of subacute bacterial endocarditis caused by enterococci, since most strains of this organism proved to be relatively more susceptible to streptomycin than to the sulfonamides or penicillin. A series of penicillin and streptomycin sensitivity studies with enterococci recovered from various sources in routine studies is listed in Table 1.<sup>1</sup> The methods used for determining penicillin and streptomycin sensitivities were modifications of the tube dilution tests of Foster and Woodruff (10) developed in our laboratory by Dr. Gregory Schwartzman.<sup>2</sup>

<sup>1</sup> We are deeply indebted to Dr. Gregory Schwartzman and Miss Beatrice Toharsky for the penicillin and streptomycin sensitivity and assay studies.

<sup>2</sup> The dilution of the materials tested is made in volumes of 1 ml. One c.c. of the

Thus it is seen that the average enterococcus in this series is 163.2 times as resistant as the standard organism to penicillin (with extremes between 5 and 300) and 35.8 times as resistant to streptomycin as the standard (with extremes between 10 and 85). Clinical experience has shown that it is well nigh impossible to treat infections with penicillin when the causative organism has a coefficient of resistance greater than 30 to 50, since the extremely high penicillin blood levels necessary cannot be satisfactorily achieved and maintained. However, a glance at the table will show that enterococci having a coefficient of resistance of 150 or 250 to penicillin may have a coefficient of resistance to streptomycin of 10 to 20. It is comparably much easier to obtain the necessary blood levels with streptomycin, which places these infections within the therapeutic range of this drug. It is evident from these observations that a blanket rule cannot be made concerning the chemotherapy of enterococcus infections. It is necessary in each instance to test the sensitivity of the infecting organism against both penicillin and streptomycin.

The enterococcus,<sup>3</sup> which occurs most commonly in the gastrointestinal tract, is a highly resistant streptococcus with distinctive characteristics. Although of low virulence, it is frequently implicated in genitourinary infections, infections associated with perforative lesions of the gastrointestinal tract, septic abortions and bacteremias in which the portal of entry is usually from the genitourinary or the gastrointestinal tract. The organism was first described by Thiercelin in 1899 (11) and the characteristics of the enterococcus group were further delineated by other investigators (12-18). The chief identifying characteristics are:

1. Streptococcal growth in ovoid pairs or short chains.
2. Ability to grow in the presence of bile.
3. Ability to ferment mannitol and salicilin but not raffinose or insulin.
4. Ability to ferment aesculin in a bile-containing medium.
5. Ability to reduce methylene blue in milk.
6. Production of a low final pH in glucose broth.
7. An unusual degree of heat resistance.

A few strains produce hemolysis. These belong to the Lancefield group D (18).

bacterial suspension containing 500-600 bacteria per ml. is used. The total test volume is 2 ml. For the determination of the penicillin levels and the susceptibility tests a meat infusion broth is used. The standard bacterium is *Staphylococcus aureus* H, which in this test is susceptible to 0.02 units of penicillin per ml. when the bacterial suspension is approximately 200-300 bacteria per ml.

For the determination of the streptomycin levels and for the test of bacterial susceptibility the meat infusion broth is diluted with distilled water. A high salt concentration is inhibitory to streptomycin. A guide to the amount of dilution is the color density of the diluted media as determined on the Lumetron photoelectric colorimeter using red filter 650. The standard bacterium used for the streptomycin susceptibility tests is *Staphylococcus aureus* SM (Smith), which is susceptible to 0.2 units of streptomycin per ml. when the bacterial suspension is approximately 250 bacteria per ml.

<sup>3</sup> In our laboratory the routine tests used for identifying enterococci are its ability to grow on Endo medium and ox bile, its ability to ferment aesculin and its resistance to 60 degrees centigrade for twenty minutes.

Subacute enterococcal endocarditis has been considered a rare disease. The first case reported in the literature was described by MacCallum and Hastings in 1899 (19). This patient was on William Osler's service at The Johns Hopkins Hospital. The organism isolated was called *Micrococcus zymogenes*. This is

TABLE 1

*Penicillin and streptomycin sensitivities of enterococci recovered from routine specimens*

PATIENT	SOURCE	PENICILLIN SENSITIVITIES		STREPTOMYCIN SENSITIVITIES	
		units/cc.	coef. of resistance*	units/cc.	coef. of resistance*
R. C.	Subphrenic abscess			4	20
A. K.	Urine	4	200	4	20
A. W.	Urine	4	200	8	40
A. G.	Urine	3	150	4	20
B. H.	Urine	4	200	2	10
P. W.	Bile	2	100	12	60
M. V.	Blood	3	150	4	20
C. B.	Urine	3	150		
R. S.	Cervix	5	250		
Dr. S.	Prostate	5	250	7	35
S. S.	Blood	5	250	4	20
P. W.	Urine			6	30
L. M.	Prostate	3	150	9	45
L. T.	Urine	0.2	10		
N. S.	Blood	4	200	12	60
I. G.	Urine	5	250		
V. D.	Blood	3	150	17	85
R. J.	Blood	4	200		
R. M.	Blood	0.1	5		
J. L.	Blood	0.5	25		
J. H.	Blood	2	100		
M. K.	Blood	4	200		
J. W.	Blood	6	300		
E. G.	Blood	2	100		
Average			163.2		35.8

\* The sensitivity of the organism under study is expressed as a coefficient of resistance in terms of comparison with the standard test organism. Thus,

$$\frac{\text{Number of units of drug per cc required to inhibit organism under study}}{\text{Number of units of drug per cc required to inhibit standard test organism}} = \text{coefficient of resistance.}$$

now recognized as belonging to the enterococci and is referred to as *Streptococcus zymogenes*, an hemolytic streptococcus belonging to the Lancefield group D. A review of the literature reveals sixty-five reported cases since this original description. The disease is probably much more common than is generally appreciated. During the last twenty years, of 624 cases of subacute bacterial endocarditis treated at The Mount Sinai Hospital, 26 were caused by enterococci,

an incidence of 3.2 per cent. An analysis of these 26 cases is of some interest. Ten were female and sixteen male. Among the females, only two were over fifty years of age, the average being 37.4 years. The youngest was twenty-three and the oldest sixty. Among the males, ten were over fifty years of age, the average being 50.5 years. The youngest was twenty-eight and the oldest seventy-five. The source of infection was traceable in ten cases to recent infection or operative manipulation of the genito-urinary tract; in four cases to infection of the gastrointestinal tract; and in one to a septic criminal abortion. The patients with enterococcus endocarditis differ, therefore, from those with *Streptococcus viridans* in that the age group is, in general, a much older one; three-fourths of the *viridans* cases occur in the third and fourth decades (1). Also, the source of the initial bacteremia is either the genitourinary or gastrointestinal tract rather than the oral cavity. The age incidence among the males particularly, seems to parallel that of genitourinary difficulties. In all the cases there were clinically demonstrable valvular abnormalities present, apparently, before the bacterial infection of the valves occurred. In this series only five post mortem examinations were done. Four of these revealed evidence of old rheumatic valvulitis with bacterial vegetations on the aortic valve in two, and on the mitral valve in two. The fifth case revealed a patent interauricular septal defect and an abnormal insertion of the anterior leaflet of the mitral valve. Vegetations in this case occurred on the aortic and mitral valves and on the auricular endocardium.

Contrary to the dramatic experiences with the penicillin treatment of *Streptococcus viridans* endocarditis, little success has been obtained in cases caused by the enterococcus group. Two cases of possible spontaneous remission are reported (20 and 21), and recently MacNeal and his coworkers (22) reported clinical arrest of a case in which penicillin and enterococcus bacteriophage were used. Among a group of forty patients treated for subacute bacterial endocarditis on the wards of The Mount Sinai Hospital since penicillin first became available to us, four were caused by the enterococcus.<sup>4</sup> They presented many of the common problems involved in the use of our newer chemotherapeutic agents. One was treated with penicillin alone, two with massive sulfonamide therapy and penicillin, and one with streptomycin alone.

#### ILLUSTRATIVE CASES

*Case 1. History.* A 51 year old white housewife was admitted to the hospital on April 12, 1944 for weakness, fever, dyspnea, orthopnea, and weight loss of three to four months' duration. In 1934 she had intermittent attacks of right upper abdominal fullness and pain, gaseous eructations and occasional mild jaundice. These symptoms disappeared spontaneously. In December, 1943, she had a sudden attack of dizziness and nausea and at this time noted a painful ecchymotic area about 3 cm. in diameter on her left foot. One week later she first experienced throbbing headaches and fever. Because of her occasional eructations and vague complaints, a gallbladder x-ray series was taken by a private physician. This is said to have revealed "stones." In March, 1944, she experienced sudden knife-like upper abdominal pain radiating to the left anterior chest and left shoulder associated with the onset of severe dyspnea and orthopnea. Later in the month she again

<sup>4</sup> Previously reported by one of us (23).



developed afternoon fever ranging 101°F. to 102°F. Two weeks before admission she saw two ecchymotic areas on her left thumb and left big toe. These were tender and measured about 1 cm. in diameter.

*Examination* on admission revealed a well developed and well nourished white middle-aged woman who appeared chronically ill. The patient coughed while recumbent. She was orthopneic, but not dyspneic or cyanotic. No petechiae were evident. The heart appeared to be enlarged to the left on percussion. The sounds were of good quality. The first mitral sound was accentuated, there were both a diastolic rumble and a systolic blowing murmur at the apex. A diastolic thrill was palpable. The second pulmonic sound was accentuated. The rhythm was regular. The blood pressure was 100 systolic and 60 diastolic. The spleen was palpable and slightly tender. Moderate clubbing of the fingers was present.

*Course.* On admission the hemoglobin was 76 per cent (Sahli); this subsequently fell to 65 per cent; the white blood count was 7,950 with a normal differential count. Her urine showed only occasional traces of albumin and microscopic hematuria. An x-ray of the chest revealed the heart to be moderately enlarged in the transverse diameter. There were no abnormalities in the lungs. A flat x-ray film of the abdomen revealed a ptosed right kidney and an irregular concretion in the gallbladder. The urea nitrogen was 26 mgm. per cent. Repeated blood cultures revealed enterococci, about 40 colonies per c.c. The organism was sensitive to 0.1 units of penicillin per c.c., i.e., five times as resistant as the standard organism.

The diagnosis of subacute bacterial endocarditis was made. It was felt that the disease was superimposed on a mitral valve deformed by antecedent rheumatic infection. Since at this time penicillin was not available in quantities adequate for therapy, the patient was discharged, to be re-admitted as soon as the drug should become available. Sulfonamides were not used because of the notorious resistance of enterococci to these chemotherapeutic agents.

Eight days later, on May 12, 1944 the patient was re-admitted for penicillin therapy. While at home she had had temperatures between 102° and 103°F. Physical examination on this admission revealed no important developments. No new embolic phenomena were evident. The hemoglobin was 64 per cent (Sahli). The red blood count was 3.7 million. The white blood count was 7,700, with normal differential. Blood cultures were again positive for enterococci. Four days after admission she developed severe right flank pain and right costovertebral angle tenderness: this was followed in several days by frankly bloody urine. These symptoms were attributed to renal infarction. On March 24th a continuous intravenous drip of penicillin was started, a total of 200,000 units being given in 24 hours. This was continued for 28 days. Concurrently the patient received heparin intravenously in doses ranging from 100 to 200 mgm. per day. This maintained her clotting time between 15 and 25 minutes. At the end of eight days of treatment with penicillin the blood cultures became sterile. Several days later the temperature became normal and clinical improvement was strikingly apparent. The blood penicillin levels varied between 0.2 and 0.8 Oxford units per c.c. of serum, the average being 0.4 Oxford units per c.c. Three days after penicillin was discontinued the fever recurred and was accompanied by chest pain and malaise. The blood culture was again positive. One week later a second course of intravenous penicillin was begun. This time the patient received 500,000 units per day by continuous intravenous drip for a period of one month. Intravenous heparin was again administered throughout this course. After two weeks the temperature became normal and remained so except for occasional evanescent spikes attributable to pyrogens in the intravenous fluids. The penicillin blood levels ranged during this treatment from 1.0 to 1.6 Oxford units per c.c. of serum. During this second course of therapy several embolic incidents, such as an Osler's node and left upper quadrant pain (splenic infarct), occurred. Subsequently the fever and all other complaints disappeared. A blood culture three days after completion of therapy was sterile. During the remainder of her hospital stay, five weeks, three blood cultures were sterile. She was discharged August 30, 1944,

apparently cured, after 3½ months of hospitalization during which time she had received a total of 19,100,000 units of penicillin.

Since discharge the patient has been seen at monthly intervals in our Follow Up Clinic and except for two moderately severe upper respiratory infections she has been well, afebrile, and asymptomatic. Twenty-eight blood cultures over a two year period have been negative. The last observation was made at our Clinic in June, 1946, two years after discharge. It is interesting to note that at this time the clubbing of the fingers had completely disappeared.

*Comment.* This case is remarkable in several respects. As far as we are aware, this is the first reported cure of enterococcus endocarditis by penicillin. Furthermore, the organism was only five times as resistant to penicillin as the standard *Staphylococcus H.*, the most sensitive enterococcus we have yet encountered (Table 1). 200,000 units of penicillin per day by constant intravenous drip produced blood levels varying between 0.2 and 0.8 units per c.c. Although the organism was sensitive to 0.1 units per c.c., this concentration of the drug over a period of one month was not sufficient to sterilize the heart valves, although two to eight times that necessary to inhibit the organism *in vitro*. The second course, which consisted of 500,000 units of penicillin daily for one month, raised the blood levels to 0.8 to 1.6 units per c.c. These levels were apparently sufficient to allow for penetration into the valves in concentration adequate to sterilize them. Heparin was used in this instance as well as in a small number of our early cases. For lack of evidence of its adjuvant value and because of the dangers inherent in its use, we later discontinued heparin therapy.

*Case 2. History.* A 27 year old Puerto Rican woman was admitted to the Hospital on July 7, 1945 with a chief complaint of dyspnea and weakness of two months' duration. Three years before admission she had developed pains in her knees and shoulder joints associated with palpitation and fever; a diagnosis of rheumatic fever was made. After this she felt well except for mild dyspnea on exertion and occasional swelling of the ankles. Two months before admission she began to have marked shortness of breath, weakness, palpitation, and moderately severe non-productive cough. One week before admission she developed chilly sensations and fever up to 102°F.

*Examination* on admission revealed a well developed and well nourished woman, who appeared to be comfortable. The veins of the neck pulsated but were not distended. The heart was enlarged to the left on percussion. The first mitral sound was snapping and the second pulmonic sound was accentuated. A questionable presystolic and a definite loud blowing systolic murmur were heard at the apex. Regular sinus rhythm was present. The blood pressure was 110 systolic and 70 diastolic. The spleen was just palpable at the costal margin on inspiration. The fingers were unmistakably clubbed. There were a few petechiae on the hard palate and several on the finger tips, which were painful.

*Laboratory data.* The hemoglobin was 75 per cent, red blood count was 4.0 million, the white blood count was 13,400 with 13 per cent eosinophiles, 54 per cent segmented polymorphonuclear cells, 6 per cent non segmented polymorphonuclear cells, 25 per cent lymphocytes, and 2 per cent monocytes. The erythrocyte sedimentation rate was 20 mm. per hour (Westergren method). Fluoroscopy of the heart revealed left auricular and left ventricular enlargement with prominence of the pulmonary conus. The electrocardiogram revealed a notched P 1 and a low and semi-inverted T 4. X-ray examination of the chest revealed mitralization of the heart and normal lung fields. The urine was essentially normal. Repeated examinations of the stool failed to reveal the presence of ova or parasites. Repeated blood cultures were positive for enterococci, 8 to 17 colonies per c.c. of

blood. The organism was found to be susceptible to 3 Oxford units of penicillin per c.c., i.e. 150 times as resistant as the standard organism (*Staphylococcus aureus H*). It was found to be resistant to 50 mgm. per cent, of sulfadiazine and sulfathiazole.

*Course.* Because of the apparent hopeless prognosis it was decided to administer massive doses of sulfonamides simultaneously with penicillin. The patient was therefore given 30 grams of sodium sulfadiazine intravenously in 600 c.c. of saline on July 18, 1945. This was followed by two grams of sulfadiazine every four hours by mouth. She reacted to the massive sulfadiazine therapy with nausea, vomiting, weakness and slight hematuria. The blood urea nitrogen rose from 11 to 33 mgm. per cent. On 7-19-45, the blood sulfonamide level was 69.6 mgm. per cent. In spite of high sulfonamide levels the fever continued, and blood cultures remained positive for enterococci. After eight days of sulfonamide therapy the drug was discontinued because of a maculopapular eruption. Pleural effusion and other signs of congestive heart failure developed at this time. Thoracentesis was performed and digitalis therapy instituted.

Penicillin therapy was then administered as follows: a single intramuscular dose of 1,000,000 units was given daily for ten days. Under this regimen the blood cultures continued to be positive. Subsequent schedules of 2,000,000 units daily in two doses intramuscularly for seven days and then 700,000 units every four hours daily intravenously for seven days likewise failed to sterilize the blood stream. The blood penicillin levels obtained with these dosage schedules were as follows:

*1,000,000 units every 12 hours intramuscularly*

20 minutes after 1,000,000 units intramuscularly—72 units per c.c. of serum

2 hours after 1,000,000 units intramuscularly—10 units per c.c. of serum

5 hours after 1,000,000 units intramuscularly—1.3 units per c.c. of serum

*700,000 units every 4 hours intravenously*

10 minutes after 700,000 units intravenously—100 units per c.c. of serum

1 hour after 700,000 units intravenously—13 units per c.c. of serum

The dose was then changed to 1,000,000 intravenously every three hours with two intercalated doses of 1,000,000 units intramuscularly daily. This was maintained for 35 days. The levels obtained were:

10 minutes after 1,000,000 units intravenously—107 units per c.c. of serum

3 hours after 1,000,000 units intravenously—5.0 units per c.c. of serum.

On this schedule the fever and embolic signs disappeared and the blood cultures became negative. However, three days after the discontinuance of penicillin, the blood cultures were again positive. The organism was now found to have increased its penicillin resistance to 175 times that of the standard organism. Streptomycin sensitivity studies at this time revealed the organism to be sensitive to 17.0 units per c.c., i.e. 85 times as resistant as the standard organism. Because of the prolonged hospital stay and the rapidly increasing despair of the patient she was discharged to the Follow Up Clinic. Since discharge, she has been admitted to another hospital and is under treatment there at the present time.

Massive sulfadiazine therapy with blood levels up to 69.6 mgm. per cent and massive penicillin therapy with a total of 405,400,000 units of penicillin in five weeks had failed to sterilize the heart valve.

*Comment.* The organism in this case was highly resistant to penicillin. A concentration of 3 units per c.c. was required *in vitro* for bactericidal effect. The last course of penicillin consisted of 10,000,000 units per day for 35 days. With this dosage, blood levels ranging from 5.0 to 107 units per c.c. were obtained, i.e. from 1.7 to 35 times the concentration considered necessary to inhibit growth *in vitro*. In spite of this intensive treatment the blood was sterile for a brief interval only. Massive administration of sulfonamide accomplished little, except to produce transient azotemia and perhaps some

prolongation of the subsequent therapeutic penicillin blood levels. After completion of the various courses of therapy the resistance of the organism had increased somewhat. This has been the experience in several of our unsuccessfully treated *viridans* cases.

*Case 3. History.* A 53 year old man was admitted to the Mount Sinai Hospital for the second time. At the age of 20, while undergoing a routine insurance examination, he had been told that he had a heart murmur. He was well until June, 1943, when he was first admitted to the Hospital. He complained of hematuria, which proved to be due to a transitional cell carcinoma of the urinary bladder. A suprapubic cystotomy was performed and radon seeds were implanted. After this he was well until March, 1944 when he noted a low grade fever associated with the appearance of painful red spots on his hands and fingers. He was then admitted to another hospital where a positive blood culture was obtained. In May of 1944 he was started on 200,000 units of penicillin with heparin, daily, by continuous intravenous drip. This was given for two weeks following which he was discharged. Five weeks after discharge he suddenly developed a severe left frontal headache followed promptly by unconsciousness. He was re-admitted to the same institution, where he remained unconscious for five days. He was then given penicillin intramuscularly every four hours, a total of 3.5 million units in seven days. This was followed by intravenous protosil for a three week period. Blood cultures remained positive, and the patient left the hospital against advice. While at home he noted weakness, peri-umbilical pain, and frequent frontal headaches. He was then admitted to the Mount Sinai Hospital for further study and penicillin therapy.

*Examination* on admission revealed a well developed and well nourished man appearing chronically ill. His temperature was 99.6°F., pulse 102, respirations 24 and blood pressure 120 systolic and 80 diastolic. The heart was enlarged to the left, the point of maximum impulse being in the sixth intercostal space at the midclavicular line. A blowing systolic and a rumbling diastolic murmur were heard at the apex. An aortic systolic murmur was heard at the base. The pulse was of good quality. Regular sinus rhythm was present. Well healed right lower quadrant and suprapubic scars were seen. The liver was palpable two fingers below the costal margin; the spleen was not palpable. There was an old petechia on the left palm and a splinter hemorrhage beneath the nail of the left forefinger. The remainder of the examination was negative.

*Laboratory data.* Repeated urinalyses revealed traces of albumin and numbers of red cells. The hemoglobin was 63 per cent. Red blood count was 3.5 million. The white blood count was 4,300 with an approximately normal differential count. The blood urea nitrogen was 20 mgm. per cent. An electrocardiogram revealed only left axis deviation. Blood cultures were positive for enterococci, two colonies per c.c. of blood. The organism was found to be sensitive to 0.5 units per c.c., i.e., 25 times as resistant as the standard organism to penicillin, and resistant to a concentration of 100 mgm. per cent of sulfadiazine, sulfamerazine, and sulfathiazole. Penicillin sensitivity studies in the presence of the sulfonamides revealed a somewhat decreased resistance. In the presence of 15 mgm. per cent of sulfathiazole, sulfamerazine, and sulfadiazine, the organism was found on three tests to be 15, 20 and 25 times as resistant as the standard organism to penicillin, respectively. With the control broth without added sulfonamides the resistance remained at 25 times that of the standard.

*Course.* During the first week of hospitalization the fever was slight, running as high as 101°F. Ten days after admission extremely tender erythematous areas appeared over the left chest and left thigh. One of these lesions was biopsied and it was found to consist of multiple mural and occlusive arteriolar thrombi without bacteria. There were, also, diffuse perivascular leukocytic infiltrations.

Because of the resistance of the organism and the inadequate supply of penicillin at that time, initial treatment consisted of large doses of sulfonamides. The patient was given



25 grams of sulfadiazine per day in divided doses. Because of extreme nausea, it became necessary to administer the drug intravenously. Blood levels up to 26 mgm. per cent were obtained, yet fever and embolic phenomena persisted. Heparin was administered in conjunction with the sulfadiazine. The blood cultures remained positive. After one week of intravenous treatment signs of left heart failure appeared, probably because of the sodium bicarbonate used to alkalinize the urine. Intravenous medication was discontinued and the heart failure was treated by means of digitalis, mercurial diuretics and the usual adjuvants. Sulfonamide therapy was discontinued.

After 6 weeks of hospitalization the treatment was changed to a continuous intramuscular drip of penicillin, 500,000 units a day, plus two extra doses of 50,000 units intramuscularly twice a day. Without the extra doses, blood penicillin levels from 1 to 1.3 units per c.c. of serum were obtained. With the extra doses, levels as high as 4.5 units per c.c. of serum were obtained up to 1½ hours after the booster doses.

After 3 weeks of penicillin therapy, blood cultures became negative but the patient's general condition deteriorated. He lost weight continually, the hemoglobin dropped and heart failure became intractable. The urine continued to contain casts, albumin, and erythrocytes, and the blood urea nitrogen rose from normal levels to 76 mgm. per cent. Penicillin was discontinued after four weeks. One week later, in spite of absence of fever and in spite of negative blood cultures, hemorrhagic macules and papules appeared on the arms, legs and hands. The platelet count at this time was 250,000 per c.c. and the bleeding and clotting times and tourniquet test were normal. However, one week later, when the hemorrhagic eruption had spread rapidly, the platelet count had fallen to 40,000 per c.c. Some of the cutaneous lesions seemed to have necrotic centers. They were not believed to be embolic, however.

In spite of all supportive measures the patient died during his eleventh week in the hospital.

*Post mortem examination* of the heart revealed the presence of bacterial vegetations on the mitral and aortic valves and on the left auricular endocardium. There was a small congenital defect in the interauricular septum and an anomalous insertion of the anterior leaflet of the mitral valve, which was displaced 1½ cm. cephalad from its usual position. The vegetations contained numerous bacterial colonies. In addition there was severe coronary arteriosclerosis with narrowing and a fresh thrombus in the right main coronary artery. The myocardium contained many focal areas of fresh and old myomalacia and an aneurysm of the posterior wall of the left ventricle. 500,000 c.c. of serous fluid were found in the left hemithorax. Pulmonary edema was present on the left and confluent bronchopneumonia on the right. There were embolic infarctions of the kidneys, spleen and testes. There was no residuum of the transitional cell carcinoma of the bladder, the site of the original lesion having been completely replaced by fibrous tissue.

*Comment.* In this case death was not directly attributable to embolism. The gradual decline in the patient's health in spite of sterilization of the blood stream is difficult to explain. It was probably due to a combination of factors, such as repeated embolization in vital organs, severe arteriosclerotic heart disease, and toxicity associated with intermittent bacteremia. The terminal episode was apparently a coronary occlusion.

The organism was a fairly sensitive enterococcus, only 25 times as resistant as the standard organism to penicillin. It is interesting to note that 600,000 units of penicillin per day for four weeks succeeded in sterilizing the blood stream, but not the vegetations. Unfortunately, adequate amounts of penicillin were not then available to permit greater dosage without deprivation to other patients. Perhaps the massive doses available today might have facilitated healing.



**Case 4. History.** A 32 year old woman was admitted for the second time to the Mount Sinai Hospital. She complained of 8 days of fever and chills, which began 2 days after an instrumental abortion. She was first admitted to The Mount Sinai Hospital in March 1941 at which time she had subacute bacterial endocarditis due to *Streptococcus viridans* superimposed on inactive mitral valvulitis. She was treated with sulfapiridine and sulfathiazole, under which regimen she became afebrile and asymptomatic and her blood cultures became sterile. She was discharged, apparently cured, on May 15, 1941. From that time up to February 11, 1946, she was apparently in good health. On February 13, 1946, ten days before the second admission, an eight-weeks pregnancy was aborted instrumentally. Two days after this procedure the patient developed malaise, chills, fever, and continuous vaginal bleeding. She was admitted on February 23, 1946 with a temperature of 105.6°F.

**Examination.** The patient was acutely ill. There were no evidences of embolism. The heart was not enlarged. A harsh, moderately intense systolic murmur was audible at the apex. The pulmonic second sound was accentuated. The spleen was not palpable. Sanguino-purulent material was emanating from the vagina. The retroposed uterus was of the size of a 6 weeks' gestation. A blood culture taken on admission revealed innumerable colonies of *Staphylococcus aureus* A in all flasks and plates. The organism was found to be sensitive to 0.1 Oxford units per c.c., i.e. 5 times as resistant as the standard organism to penicillin. The admission diagnosis was septic abortion with bacteremia and inactive rheumatic heart disease with mitral stenosis and insufficiency. Penicillin was given immediately, 50,000 units intramuscularly every three hours. When the result of the blood culture was obtained the next day, the penicillin dosage was increased to 100,000 units every three hours. The blood count was: hemoglobin 38 per cent, red blood cells 2.2 million, white blood cells 14,800 with 59 per cent segmented polynuclear cells and 34 per cent non segmented polymorphonuclear cells, 14 per cent lymphocytes and 3 per cent monocytes. The erythrocyte sedimentation rate was 103 mm. per hour by the Westergren method. The urine was essentially normal. An electrocardiogram revealed regular sinus rhythm, left axis deviation and no evidence of myocardial damage. Roentgen examination of the chest revealed enlargement of the heart with mitralization. The cervical discharge was found to contain *Staphylococcus aureus* A and enterococci.

**Course.** The patient was treated by means of the blood transfusions and continued penicillin administration intramuscularly. On the third hospital day her temperature dropped to 99.6°F. and continued for the next week between 99° and 100°F. On the fifth hospital day a blood culture was sterile. On the tenth day penicillin was discontinued for 24 hours and a blood culture was taken. Enterococci grew out in all flasks in a concentration of 15 organisms per c.c. Another blood culture two days later while again under penicillin therapy, yielded enterococci in the same concentration. This organism was found to be 150 times as resistant as the standard organism to penicillin (susceptible to 3.0 Oxford units per c.c. of media), and 20 times as resistant as the standard organism to streptomycin (susceptible to 4.0 units per c.c. of media). A total of 11,950,000 units of penicillin was administered over a period of 25 days, with no appreciable effect on the enterococcemia. In spite of the continuance of penicillin therapy, at the beginning of the second week the temperature rose to 101°F. and at the beginning of the third hospital week the temperature ranged between 101° and 103.6°F. The spleen was now palpable two fingerbreadths below the costal margin. Blood cultures on the 16th and 23rd days were again positive, 50 colonies per c.c. A gynecological consultation revealed the presence of a slight amount of vaginal bleeding. The cervix was closed and firm. The uterus was small, anteflexed and easily movable. The adnexae and parametria were normal. This examination was performed on March 6, 13 days after admission. It was the opinion of the consulting gynecologist that the pelvis was no longer the site of the feeding focus of infection. A uterine culture was obtained at this time and found to be sterile. The sequence of events was interpreted as follows:

In consequence of instrumental abortion the pelvic organs were infected with an hemolytic *Staphylococcus aureus* and an enterococcus with resulting bacteremia with both organisms. On admission, a blood culture revealed innumerable colonies of staphylococcus

aureus on all plates. The staphylococcus aureus bacteremia was controlled by the penicillin. The resistant enterococcus, which had become implanted on the site of the previously diseased heart valves at the onset of the blood invasion, reappeared in the blood stream seven days following recovery from staphylococcemia.

Although the enterococcus in this case was relatively resistant to streptomycin, it was felt that, in view of the recent deposition on the heart valve, a trial of streptomycin was indicated. This was begun on the 23rd hospital day. Blood cultures on the 16th and 23rd hospital days had revealed enterococci in a concentration of 50 organisms per c.c. The drug was given intramuscularly in doses of 1 gram (1 million units) every six hours for 5 days, or a total of 20 grams (20 million units). It was administered in 1 per cent novocaine, (0.5 grams were dissolved in 4 c.c. and 2 doses given simultaneously, one in each buttock). The only toxic manifestation noted was oliguria on the 5th day of streptomycin administration. The 24 hour output of urine on that day was 300 c.c., whereas it had ranged between 600 and 1200 c.c. on the preceding days. There were no abnormal findings in the urine and the oliguria cleared by the next day. A blood culture toward the end of the first day of streptomycin therapy was sterile. Six subsequent cultures on the 26th, 27th, 28th, 32nd and 36th hospital days were all negative although cystine, a streptomycin deactivator, was used in the culture medium. Streptomycin blood levels ranged between 25 and 50 micrograms<sup>5</sup> per c.c. and urine levels between 600 and 200 micrograms per c.c. The drug was detectable in the urine 3 days after discontinuance of therapy at levels of 8 micrograms per c.c.

On the first day of therapy the temperature fell from 103.6° to 98.6°F. It ranged between 99° and 100.6°F. during the period of treatment and promptly fell to normal thereafter and remained so throughout the subsequent period of observation, 21 days. There was marked subjective and objective improvement with weight gain and a feeling of well being. The spleen remained palpable just below the costal margin. On April 10, 1946, after 49 days in the hospital, the patient was discharged, apparently cured.

She was then seen at our Follow Up Clinic at monthly intervals. For three months she was afebrile and symptom-free, and repeated blood cultures were sterile. However, shortly thereafter she noted an evening temperature rise up to 101°F., associated with mild malaise and anorexia. This was present for ten days before she presented herself for readmission to the hospital on July 15, 1946.

Examination at this time revealed essentially the same findings. The spleen was enlarged two fingerbreadths below the costal margin. There was no evidence of embolism. Blood cultures now revealed the presence of enterococci again, about 20 colonies per c.c. The character of the organism had changed somewhat. Whereas previously it had grown within 24 hours, it now required three days to grow out in discernible numbers. Surprisingly, the organism now was as sensitive as the standard organism to streptomycin; its resistance was now  $\frac{1}{10}$  that of its original resistance. Streptomycin therapy was therefore resumed in doses of 0.25 grams every 6 hours intramuscularly, a total of 1.0 grams per day. This was continued for 14 days. However, in spite of blood levels of about 10 micrograms per c.c. of serum, blood cultures remained positive and temperatures ranged between 99° and 100°F. The organism was now found to be 6 times as resistant as the standard to streptomycin. The dose of the drug was then increased to 0.5 grams every 6 hours. This was maintained for six days, in spite of which the blood cultures remained positive. The organism was now ten times as resistant as the standard. The dose of streptomycin was then raised to 4.0 grams daily, divided in four doses, for a period of 5 days. Blood levels with this dosage schedule ranged between 30 and 60 micrograms per c.c. of serum. In spite of these tremendous levels blood cultures remained positive. A total of 41 grams of streptomycin was used over a period of one month without any effect upon the clinical course. At the time of writing, the patient is still in the hospital, with fever ranging between 100

<sup>5</sup> One microgram of streptomycin equals 1 unit.

and 102°F. There are occasional Osler's nodes. The blood cultures are persistently positive for enterococci with a streptomycin resistance of 10 times that of the standard organism. Because of the streptomycin shortage, it is contemplated to defer further therapy until such time as enough of the drug has accumulated to allow of massive dosage. This appears to be the only hope of cure.

There are several very significant features in this case. The initial treatment with streptomycin was begun, apparently, a short time (approximately two weeks) after the organism had implanted itself upon the heart valves. A five day intensive course, using a total of 20 grams of streptomycin, was sufficient to cause complete clinical remission for a period of three months, in spite of a relatively resistant organism. This short course apparently failed to sterilize the deep regions of the valvular interstitium. This duplicates our experience with penicillin-treated cases in which we found smaller doses over a longer period of time (five weeks) much more efficacious in producing permanent cures than massive doses over a short period of time. We have reason to believe that a permanent cure would have been effected had the initial streptomycin course of 4.0 grams per day been continued for four to five weeks. Unfortunately the limited supply of the drug precluded this. A permanent cure with a third streptomycin course now appears extremely doubtful. Should the supply become plentiful, it will be attempted.

If the organism which caused the remission was the same as that which caused the initial attack, it had changed its characteristics in a manner difficult to explain. Not only did it now require two days longer to grow out in culture, but its resistance had decreased twentyfold. Yet despite this increase in sensitivity, streptomycin blood levels many times the *in vitro* bactericidal level failed to sterilize the blood stream. For this there are two possible explanations. Either the bacteria had become too deeply imbedded in necrotic valvular tissue (24) to allow for adequate penetration of streptomycin, or the organism had changed so as to produce a discrepancy between the sensitivities *in vitro* and *in vivo*. This latter phenomenon has been reported (25).

During the second streptomycin course the resistance of the organism increased tenfold. This phenomenon has been described in other inadequately treated cases, especially with infections of the genitourinary tract (26).

The only toxic manifestation which might be ascribed to streptomycin was oliguria for one day.

The remarkable feature in this case is that at various times the patient was treated successfully for three otherwise fatal blood stream infections caused by three different specific agents: a *Streptococcus viridans* endocarditis cured with sulfonamides, a *Staphylococcus aureus* bacteremia eradicated by penicillin, and an enterococcus endocarditis driven into temporary remission by streptomycin.

#### DISCUSSION

Among the 25 per cent of the subacute bacterial endocarditis cases that remain unsuccessfully treated, a major portion are caused by exceptionally

resistant organisms. The enterococcus is the most frequent offender in this resistant group. The marked penicillin resistance of most of these bacteria precludes even massive therapy with this substance. It seems likely that a number of these cases may be amenable to streptomycin because the organisms are relatively more sensitive to this drug. Sensitivity studies are of paramount importance before treatment is begun, for not only the choice of the drug, but also the dosage will be suggested by these determinations. It has been adequately shown that in undertreated cases the resistance of the organism may be increased. This is especially true with streptomycin.

It is extremely important that the choice of drug and the proper dosage be made as soon as possible so that treatment may be initiated in time to avoid irreparable valvular damage. A rather frequent complication which defies all treatment is mycotic aneurysm of the sinus of Valsalva, with extension of the infection into the pericardium. In our experience this complication is the result of procrastination and inadequate dosage. It has been invariably fatal. We have also found that inadequate doses may sterilize the blood stream and apparently the surfaces of the affected valves, without affecting the clinical course, or ridding the interstices of the vegetations of the organisms. It is a common practice of family physicians to try a little penicillin therapy before referring the patient with subacute bacterial endocarditis to the hospital. This makes further recovery of the bacteria from the blood stream and the evaluation for therapy more difficult.

#### SUMMARY

Four cases of enterococcal subacute bacterial endocarditis are reported. In one case cure was obtained by means of penicillin alone. In another a temporary remission was obtained by means of streptomycin alone. In the two remaining cases penicillin was combined with massive doses of sulfonamides; the result was complete failure. The following conclusions are drawn:

1. Sensitivity studies must be performed, since such studies guide the physician in the choice of drugs.
2. Treatment should be instituted as early as possible, in order to avoid damage to the heart and embolism of the visera.
3. The drug of choice should be used to the limit of tolerance for at least five weeks.
4. Though the minimal serum level of penicillin or sulfadiazine should be five times the minimum *in vitro* concentration required for complete bacteriolysis, the relations between the optimum serum level of streptomycin and the *in vitro* concentration required for bacteriolysis is less well defined and probably varies with different bacterial strains.

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# CASTRATION COMBINED WITH TESTOSTERONE TREATMENT AFTER MASTECTOMY FOR BREAST CANCER

## ENDOCRINOLOGICAL AND METABOLIC CHANGES

I. SNAPPER, M.D.

(New York, N. Y.)

*From the Second Medical Service of the Mount Sinai Hospital*

It has been recognized for some years that there is a relation between ovarian function and development and the spread of mammary cancer.

Ever since Schinzinger (1) advised bilateral oophorectomy in women with malignant breast tumors, the problem of castration in mammary carcinoma has been studied both by surgeons and roentgenologists. Some of the more important contributions on this subject were reviewed by Leucutia (2).

The early publications on the favorable effect of surgical castration in women with breast cancer received belated recognition in 1930 when Ahlbom (3) reported on the regression of bone metastasis from breast cancer after x-ray castration. His conclusions have been confirmed in recent publications (4). Adair and associates report 13 to 15 per cent of cases with metastases improved either after surgical or x-ray castration (5).

In addition to this palliative measure, reports on the beneficial influence of testosterone propionate on metastatic breast cancer deserve special attention. Since 1939, it has become known that considerable relief from pain can be obtained in many patients with bone metastases secondary to mammary cancer by parenteral treatment with this hormone. Ulrich (6) is probably the first who utilized testosterone in the treatment of mammary cancer. Loeser (7) reported that gratifying results attended the use of testosterone propionate in three patients with recurrence of cancer after a previous radical mastectomy. Farrow and Woodard (8) treated 33 cases with skeletal metastases from breast cancer with testosterone propionate. Relief from pain was obtained in about one-half of the patients. Fels (9) reported favorable results with testosterone propionate in the treatment of three patients with mammary carcinoma.

Adair and Herrmann (10) recently observed remarkable improvement in four of eleven patients who had advanced breast cancer and were treated with larger amounts of testosterone propionate. Of the four patients who benefited from this treatment, one had soft-part and three, osseous metastases. In the first patient the primary lesion and the soft-part metastases regressed, in the three other patients recalcification of the osseous metastases coincidental with disappearance of pain could be observed. In apparent contrast to these results, it should be mentioned that inhibitory influence of synthetic estrogens on the growth of mammary cancer has also been reported (10 and 11).

It should be stressed that, in general, only temporary relief can be obtained in patients suffering from breast cancer with metastases either by surgical or x-ray

castration or by the use of testosterone. Clinical or x-ray evidence of an actual cure is only rarely obtained, and the same holds true for prolongation of life.

Recently, both castration and testosterone administration have been used, not so much for the treatment of metastases of breast cancer but for the prevention of metastasis in women who had undergone radical mastectomy. This preventive treatment seemed justified in view of the data obtained by animal experimentation. Early castration of female mice, belonging to strains characterized by a high percentage of spontaneous mammary cancer, reduces the incidence of cancer (12). On the other hand, administration of estrogen increases the incidence of spontaneous cancer in strains characterized by a low percentage of mammary tumors (13). Finally, there is reason to believe that the administration of testosterone to mice belonging to a cancerous strain reduces the incidence of cancer (14). It is unnecessary to say that the results of animal experimentation cannot be applied directly to humans; it is well known that mammary cancer also occurs in women who had undergone previous surgical castration.

Notwithstanding the latter experience, Horsley (15) performed bilateral oophorectomy in twenty-five women with breast cancer in the premenopausal age immediately after radical mastectomy in order to prevent the formation of metastasis. Whereas x-ray castration immediately after mastectomy has not resulted in an appreciable decrease of metastasis formation or increase of life expectancy, Horsley's initial figures seemed to indicate that by surgical castration, the formation of metastases could at least be delayed. A later follow-up, however, was less promising (16).

Encouraged by the initial results of Horsley we decided in 1944 to intensify the possible preventive influence of castration on the development of metastases by combining castration with the administration of testosterone propionate. It seemed reasonable to assume that as far as the prevention of metastasis is concerned, the combination of both these methods of treatment might be more effective than either castration or testosterone treatment alone. There is some evidence that the adrenal cortex may elaborate estrogen after removal of the ovaries. Thus, even after surgical castration, neutralization of estrogen production remains necessary.

After we had started our experiments in this field, Prudente (17) reported on the results of the administration of testosterone propionate in patients with breast cancer after mastectomy. He presented his findings in 63 patients with breast cancer who received testosterone propionate as a postoperative measure for prevention of recurrences. As controls, he used 63 patients who had undergone radical surgery but in whom no androgenic therapy was employed. The author concludes that results with testosterone propionate "are about 100 per cent better than those observed after operation only."

#### PLANNING OF CLINICAL RESEARCH

Up to October 1946, surgical castration had been performed on 22 women after mastectomy, and this was followed by testosterone propionate injections.

Fifteen of these patients had axillary metastases at the time of the mastectomy.

In seven other patients the axillary nodes were found to be normal at the time of the operation. In none of the cases were tumor cells found in the ovaries. The ages of these patients ranged between 31 and 49 years at the time of the mastectomy. In addition two patients in whom carcinoma of the mammary gland developed after a previous oophorectomy have also been treated with testosterone propionate. These two patients are not discussed in this paper.

In order to ascertain whether differences exist between surgical castration and

TABLE I

*Surgical castration and testosterone treatment after mastectomy in patients with axillary metastasis*

PATIENT	AGE	MASTECTOMY	SURGICAL CASTRATION	PERIOD ELAPSED BETWEEN MASTECTOMY & CASTRATION	TESTOSTERONE STARTED	AXILLARY LYMPHNODES
W. R.	41	March '44	Aug. '44	5 months	Sept. '44 <sup>2</sup>	+
V. M.	41	Oct. '43	Oct. '44	12 months	Nov. '44 <sup>1</sup>	+
R. S.	46	April '43	Nov. '44	19 months	Dec. '44 <sup>2</sup>	+
S. M.	42	July '44	Dec. '44	5 months	Dec. '44 <sup>1*</sup>	+
R. B.	37	Aug. '44	Dec. '44	4 months	Dec. '44 <sup>1†</sup>	+
M. E.	40	Feb. '43	Jan. '45	23 months	Jan. '45 <sup>2</sup>	+
E. W.	45	Feb. '44	Mar. '45	4 months	Oct. '44 <sup>1</sup>	+
H. G.	34	Feb. '45	Mar. '45	1 month	May '45 <sup>1</sup>	+
S. G.	44	Feb. '45	Apr. '45	2 months	May '45 <sup>1</sup>	+
M. R.	34	Apr. '45	Apr. '45	$\frac{1}{2}$ month	May '45 <sup>1</sup>	+
S. J.	48	Mar. '45	May '45	2 months	Aug. '45 <sup>1</sup>	+
B. M.	31	Oct. '45	Oct. '45	$\frac{1}{2}$ month	Nov. '45 <sup>2‡</sup>	+
A. R.	42	Oct. '45	Dec. '45	2 months	Dec. '45 <sup>1§</sup>	+
M. L.	47	Nov. '45	Mar. '46	4 months	Apr. '46 <sup>1</sup>	+
B. R.	49	May '46	May '46	$\frac{1}{2}$ month	June '46 <sup>2</sup>	+

<sup>1</sup> Three months of 3 weekly injections of 25 mg. Neo-Hombreol. Two months interval. Two months of one weekly injection of 25 mg. Neo-Hombreol. Two months interval. Two months of one weekly injection of 25 mg. Neo-Hombreol. To be repeated yearly.

<sup>2</sup> Three months of 3 weekly injections of 25 mg. Neo-Hombreol. Two months interval. Two months of 2 tablets of methyl testosterone by mouth. The administration of methyl testosterone to be repeated regularly.

\* Developed a carcinoma in the other breast with axillary metastases in January 1946.

† December 1946 metastases in the pleural cavity.

‡ September 1946 generalized metastases.

§ November 1946 generalized metastases.

x-ray castration, in seven women irradiation of the ovaries followed by testosterone propionate treatment was performed after the mastectomy (table II). The ages of these patients ranged between 21 and 53 years at the time of the operation. In some of the older patients menstruation had already stopped shortly before the x-ray treatment. Irradiation of the lower abdomen was performed nevertheless in order to destroy remnants of functioning ovarian tissue. In all but one of these seven patients involvement of the axillary lymph nodes was found at the time of operation.

In the entire series, testosterone propionate\* treatment was instituted as soon as possible after castration. Each patient received 25 mg. of the hormone intramuscularly three times a week for a period of three months. This series was followed by an interval of one to two months without therapy. In all the patients who received x-ray castration and in 13 of the surgically castrated patients, testosterone treatment was resumed in dosages of 25 mg. administered intramuscularly once a week for two months. After a rest period of two months, 25 mg. was given once a week for two months. Then treatment was discontinued for one month. This plan of treatment starting with a three month period of three weekly injections is repeated every year.

In 9 of the surgically castrated patients, the initial series of three months of three weekly injections of 25 mg. of testosterone propionate was followed by an

TABLE II

*Surgical castration and testosterone treatment after mastectomy in patients without axillary metastasis*

PATIENT	AGE	MASTECTOMY	SURGICAL CASTRATION	PERIOD ELAPSED BETWEEN MASTECTOMY & CASTRATION	TESTOSTERONE STARTED	AXILLARY LYMPHNODES
B. M.	39	Feb. '41	Aug. '44	42 months	Oct. '44 <sup>2</sup>	—
I. S.	48	May '43	Dec. '44	19 months	Jan. '45 <sup>2</sup>	—
I. W.	46	June '45	June '45	0 months	June '45 <sup>2</sup>	—
R. D.	38	Aug. '45	Aug. '45	$\frac{1}{2}$ month	Sept. '45 <sup>1</sup>	—
G. S.	46	Dec. '45	Jan. '46	1 month	Mar. '46 <sup>2</sup>	—
M. L.	38	Aug. '46	Aug. '46	0 month	—	—
I. Z.	42	Mar. '41	Apr. '46	61 months	May '46 <sup>2</sup>	—

<sup>1</sup> Three months of 3 weekly injections of 25 mg. Neo-Hombreol. Two months interval. Two months of 1 weekly injection of 25 mg. Neo-Hombreol. Two months interval. Two months of 1 weekly injection of 25 mg. Neo-Hombreol. To be repeated yearly.

<sup>2</sup> Three months of 3 weekly injections of 25 mg. Neo-Hombreol. Two months interval. Two months of 2 tablets of methyl testosterone by mouth the administration of methyl testosterone to be repeated regularly.

interval of two months without treatment. Thereafter, 20 mg. of methyl testosterone was given by mouth for two months. From then on, two months without treatment was regularly followed by two months of peroral methyl testosterone ingestion.

Despite the restricted period of observation, it can already be stated that the combination of castration with testosterone treatment does not protect the patients after radical mastectomy.

#### CLINICAL RESULTS

In all patients who were selected for this treatment careful x-ray examination revealed absence of metastases in lungs, lumbosacral spine and pelvis before the treatment started.

\* The testosterone propionate used in this study was supplied in the form of *Neo-Hombreol* by Roche Organon, Inc., Nutley, N. J., through the courtesy of Dr. Leo Pirk.

Of the 15 patients in whom axillary metastases were found at the time of the mastectomy, two have been followed for less than a year before the surgical castration (table I). This leaves 13 patients with carcinoma of the breast and axillary metastasis who have been observed for more than one year after the mastectomy followed by surgical castration and testosterone propionate. In two of these patients the time between mastectomy and oophorectomy has been longer than one year (19 months and 23 months respectively).

Of these 13 patients, 4 have already developed new manifestations of carcinoma.

*Case 1.* Mrs. S. M. was 42 years of age when she was operated upon in July 1944 for carcinoma of the right breast with metastasis to the axillary lymph nodes. She received x-ray treatment to the right chest wall, over the supraclavicular area and the right axillary groove between November 8, 1944 and November 20, 1944, a total of 2,000 R in air. In December, 1944, five months after the mastectomy, surgical castration was performed. Testosterone propionate was injected in doses of 25 mg.

December, 1944 to March 7, 1945, 36 injections.....	900 mg.
April 4, 1945 to May 26, 1945, 8 injections.....	200 mg.
July 11, 1945 to Sept. 12, 1945, 8 injections.....	200 mg.
Dec. 5, 1945 to Dec. 31, 1945, 10 injections.....	250 mg.

In January, 1946, after she had received 1,550 mg. of testosterone propionate in the course of 13 months, a tumor in the left mamma adherent to the skin was discovered. Operation showed this to be an infiltrating scirrhous carcinoma with metastasis to the axillary lymph nodes. After the second operation generalized metastases were discovered in July, 1946. During the testosterone propionate treatment the signs of masculinization were not marked but a certain amount of hoarseness and a slight growth of hair on the face developed.

*Case 2.* Mrs. B. M., aged 31 years, was delivered of a child in July 1945. Four weeks after the delivery, during the period of breast feeding, she felt a lump in the left breast. Six weeks later, on October 12, 1945, a radical mastectomy was performed. An infiltrating scirrhous carcinoma with involvement of the lymph nodes was found. Two weeks later, bilateral salpingo-oophorectomy was performed. Following operation she received x-ray radiation over the operative field and injections of testosterone propionate. Unfortunately, in this case the schedule of injections was not adhered to strictly. She received only 18 injections of 25 mg. of testosterone propionate during November and December 1945. No hirsutism or hoarseness developed. After this short series of testosterone propionate injections no treatment was given for one month. Then for two months the patient received two tablets of 10 mg. methyl testosterone daily. Again the treatment was stopped for one month, followed by daily administration of two tablets of 10 mg. methyl testosterone for two months. One month later metastases were discovered in the supraclavicular lymph nodes and in the mediastinum.

*Case 3.* Mrs. A. R., aged 40 years, was admitted on October 8, 1945 because she had discovered a small non-tender nodule in the right breast six months previously. At operation on October 11, 1945 a scirrhous carcinoma with extensive lymph node involvement was found. On November 26, 1945, a bilateral salpingo-oophorectomy was performed. Testosterone propionate was injected in doses of 25 mg.

December 8, 1945 to March 25, 1946, 36 injections.....	900 mg.
June 5, 1946 to July 22, 1946, 8 injections.....	200 mg.
Sept. 20, 1946 to Nov. 6, 1946, 8 injections.....	200 mg.

During the treatment with male hormone the signs of masculinization were only slight. By November 9, 1946, after she had received 1,300 mg. of testosterone propionate in the



course of eleven months, a local recurrence had developed in the operative scar near the apex in the axilla and several local recurrences in the chest wall. A small right supraclavicular node anterior to the trapezius muscle was also present. In addition, there was a large mass infiltrating the left breast and there were large axillary nodes at the left side.

*Case 4.* Miss R. B., aged 36 years, was admitted on August 25, 1944. For two years she had observed a mass in the right breast. Three weeks before admission patient noticed painful sensations in the mass. There was a walnut-sized, stony hard mass in the outer quadrant of the right breast. In the right axilla a hard node was found. At operation a scirrhus carcinoma with involvement of the axillary nodes was found. In November 1944, bilateral salpingo-oophorectomy was performed.

Testosterone propionate was injected in doses of 25 mg.

Dec. 17, 1944 to March 30, 1945, 36 injections.....	900 mg.
May 25, 1945 to July 11, 1945, 8 injections.....	200 mg.
Sept. 19, 1945 to Nov. 14, 1945, 8 injections.....	200 mg.
Jan. 16, 1946 to April 10, 1946, 36 injections.....	900 mg.
June 24, 1946 to Aug. 21, 1946, 8 injections.....	200 mg.

During the course of treatment patient had moderate but not marked hirsutism and hoarseness. In August, 1946, after she had received 2,400 mg. of testosterone propionate in the course of 20 months, she started to complain of pain in the right chest. She had some difficulty in breathing. X-ray of the chest was negative but the sedimentation rate of the red blood cells was markedly increased. In December 1946 a hemorrhagic effusion developed in the left pleural cavity.

Perhaps it is of some importance to observe that these four patients showed only few signs of masculinization during the testosterone treatment.

For completeness it should be mentioned that at the present writing the two patients of the same group who have been observed for a period of less than one year after castration and testosterone treatment have not developed metastases up to the present time. The same holds true for the seven patients who were treated in the same way for carcinoma of the breast without axillary metastasis (table II).

Of the seven patients who after mastectomy were treated with x-ray castration followed by testosterone injections one has developed metastasis in the chest wall and in the supraclavicular lymph nodes (table III). This occurred 18 months after irradiation of the lower abdomen and male hormone treatment had been started. This patient had then received 2,250 mg. of testosterone propionate. A second patient of this series died of encephalitis. At autopsy no metastasis could be found.

Modern statistics indicate that 70 per cent of the patients without axillary metastasis and 40 per cent of the patients with axillary metastasis survive more than 5 years after radical mastectomy. In this small series of 13 patients with axillary metastasis who after surgical castration were treated with male hormone injections four have developed metastasis within two years. In one of these patients where the outlook was unfavorable from the beginning because the mammary tumor had developed during lactation, the treatment with male hormone was given in a desultory way only.

It may be of value to comment upon certain changes which have been observed in the patients who have been treated in this way.

## ENDOCRINE CHANGES

We fully realized that the combination of castration with testosterone administration would lead to a considerable degree of masculinization.

It is generally accepted that testosterone propionate administered in doses between 250 and 300 mg. per month hardly ever causes signs of masculinization. This undesirable side effect is said to occur in only one per cent of patients treated with such doses (18). The much higher incidence of arrhenomimetic effects in the present series can probably be attributed to the combined effect of hormone and castration.

Most authors who have used testosterone propionate either for the prevention or for the cure of metastases of breast cancer have tried to avoid masculinization. Prudente (17) at the start of his work was afraid of virilization, especially in young women. As his study progressed, this fear was abandoned because it

TABLE III  
*X-ray castration and testosterone treatment after mastectomy*

PATIENT	AGE	MASTECTOMY	IRRADIATION OF OVARIES	PERIOD ELAPSED BETWEEN MASTECTOMY AND CASTRATION	TESTOSTERONE STARTED	AXILLARY LYMPHNODES
C. S.	38	Sept. '43	August '44	11 months	Sept. '44	+
A. C.	48	Sept. '44	Sept. '44	$\frac{1}{2}$ month	Oct. '44	+
D. R.	21	April '44	Nov. '44	6 months	Nov. '44	+
R. M.	45	May '44	Oct. '44	5 months	Oct. '44*	+
M. J.	43	Jan. '45	Feb. '45	1 month	Feb. '45	—
M. B.	50	March '45	May '45	2 months	May '45	+
A. S.	53	May '45	June '45	1 month	June '45†	+

\* Developed metastases in chest wall and in supraclavicular nodes in April 1945.

† Died of encephalo-myelitis in September 1946. At autopsy no metastases were found.

was realized that the symptoms of virilization are of secondary importance in cancer. A mild degree of masculinization occurred in a comparatively small percentage of Prudente's cases. The severe cases developed hypertrophy of the clitoris and hypertrichosis; the moderate ones had excessive hair growth only. No change in the character of the voice was ever noted.

In this connection it should be realized that in order to obtain optimal results, it may be necessary to change the endocrinological balance of the female body to such an extent that definite masculinization is produced. In fact, prevention of metastasis may well depend upon the degree of masculinization.

After mastectomy, surgical or x-ray castration followed by testosterone propionate treatment in triweekly doses of 25 mg. gives rise in most women to signs of masculinization in the form of hair-growth, especially on the face, sometimes on other parts of the body. Hoarseness is nearly constant and women who were accustomed to sing become unable to do so. Most of the patients treated in this way are considered by their friends and relatives to be suffering from a chronic

cold. Occasionally excessive vaginal secretion causes complaints and in about one third of the cases there is considerable increase of libido (19 and 20). The signs of masculinization, especially the hirsutism, usually disappear or at least diminish considerably in about a month following cessation of the intensive testosterone therapy and do not return to any degree during the months when only 25 mg. of testosterone propionate are given once a week.

It is remarkable that the obvious psychological distress caused by these side effects can practically always be overcome by moral persuasion and by emphasizing the following rationalization: "mammary tumors are mainly a feminine characteristic, and therefore, a certain amount of masculinization is a logical treatment to improve the chances for complete cure". The facts about mammary cancer have been so well popularized that the women who were chosen for this treatment were willing to make this sacrifice in order to improve their chances for a complete cure. Bleaching creams and depilatories may be used effectively at the time when hirsutism is most marked. Many private patients resort to electrolytic depilation. The prospect that the effects of the masculinizing hormone will greatly diminish after the three months of intensive treatment are completed brings great consolation to the patient.

Most women feel remarkably well during the testosterone treatment, and the signs of the menopausal syndrome, particularly flushes, are kept completely in check during the injections of male hormone.

#### INFLUENCE ON CALCIUM METABOLISM

In most individuals testosterone injections have a calcium sparing effect, and during the treatment with this hormone, the calcium balance becomes positive (21). However, Farrow and Woodard (8) have reported that administration of large quantities of testosterone propionate in women with breast cancer, bone metastases, and hypercalcemia has given rise to a hypercalcemia and a negative calcium metabolism. This experience has been confirmed by Adair and Herrmann (10). These authors conclude that testosterone is contraindicated in patients with osseous metastases. If however, patients with hypercalcemia associated with metastases after mammary carcinoma showed normal values for calcium and phosphorus of the blood serum no hypercalcemia was elicited by the testosterone treatment.

Table IV shows the results of testosterone treatment upon the calcium and phosphorus metabolism of our patients. It should be stressed that the doses of testosterone used in our series were much smaller than those which Farrow and Woodard or Adair and Herrmann administered. Furthermore, our patients had no detectable bone metastasis.

It follows from Table IV that testosterone administered in the quantities employed by us does not lead to hypercalcemia in castrated women operated upon for mammary cancer. There were slight variations in the calcium figures in both directions which are not significant.

The inorganic phosphorus of the blood did not change. In several cases, the alkaline phosphatase of the serum showed a tendency to increase slightly. This

was also found in two cases treated by Adair and Herrmann. Additional data seem to indicate that even this moderate increase is only temporary. The 24-hour urinary calcium excretion on a mixed diet without milk or cheese varied within the normal limits.

#### BLOOD PRESSURE FINDINGS

Blood pressure readings showed no significant change during the period of testosterone treatment as compared with pre-medication findings, except for one

TABLE IV

*Influence of a three-month period of triweekly intramuscular testosterone injections in women castrated after mastectomy*

K.A.—King Armstrong Units

B.U.—Bodansky Units

(Before and after 3 Months of Triweekly Testosterone Injections)

PATIENT	AGE	CALCIUM MGMS. $\%$		PHOSPHORUS MGMS. $\%$		PHOSPHATASE UNITS (PER 100 cc.)		CALCIUM 24 HOURS URINE	
		Before	After	Before	After	Before	After		
R. B.	36	11.1	11.0 <sup>2</sup>	5.0	3.7 <sup>2</sup>	10.0 K.A.	11.0 K.A. <sup>2</sup>	142 <sup>1</sup>	Surgical castration
E. W.	45	11.6	9.1 <sup>2</sup>	3.7	3.5 <sup>2</sup>	16.0 K.A.	12.0 K.A. <sup>2</sup>	239 <sup>1</sup>	
S. M.	42	9.7	11.8 <sup>2</sup>	4.0	4.0 <sup>2</sup>	8.5 K.A.	15.0 K.A. <sup>2</sup>	333 <sup>1</sup>	
M. R.	41	9.7	9.7 <sup>3</sup>	3.1	3.3 <sup>3</sup>	2.8 B.U.	8.4 B.U. <sup>3</sup>	300 <sup>1</sup>	
V. M.	41	11.2	11.5 <sup>2</sup>	?	2.5 <sup>2</sup>	11.0 K.A.	10.0 K.A. <sup>2</sup>	129 <sup>1</sup>	
M. E.	42	9.9	10.1 <sup>2</sup>	3.5	3.0 <sup>2</sup>	3.6 B.U.	9.0 B.U. <sup>2</sup>	245 <sup>1</sup>	
B. M.	39	10.1	9.3 <sup>2</sup>	2.9	3.5 <sup>2</sup>	4.0 B.U.	9.0 B.U. <sup>2</sup>	146 <sup>1</sup>	X-ray castration
A. S.	53	12.0	10.4 <sup>2</sup>	3.7	2.1 <sup>2</sup>	8.0 K.A.	7.0 K.A. <sup>2</sup>	152 <sup>1</sup>	
A. C.	48	9.4	11.4 <sup>2</sup>	3.3	3.2 <sup>2</sup>	11.0 K.A.	12.5 K.A. <sup>2</sup>	265 <sup>1</sup>	
M. J.	43	10.0	9.0 <sup>2</sup>	6.0	4.3 <sup>2</sup>	7.0 K.A.	6.0 K.A. <sup>2</sup>	?	
D. R.	21	11.0	12.0 <sup>2</sup>	3.0	2.7 <sup>2</sup>	8.0 K.A.	9.0 K.A. <sup>2</sup>	155 <sup>1</sup>	
R. M.	50	9.2	12.0 <sup>2</sup>	3.0	3.7 <sup>2</sup>	9.0 K.A.	9.5 K.A. <sup>2</sup>	204 <sup>1</sup>	
C. S.	38	10.5	11.8 <sup>2</sup>	4.0	4.0 <sup>2</sup>	9.0 K.A.	15.0 K.A. <sup>2</sup>	232 <sup>1</sup>	

<sup>1</sup> On a mixed diet without milk or cheese.

<sup>2</sup> Immediately after a series of 3 months of triweekly injections of 25 mg. testosterone propionate.

<sup>3</sup> Immediately after 3 months of triweekly injections of 25 mgm. testosterone propionate and 2 months of 3 methyl testosterone tablets by mouth.

patient who had a tendency to hypertension before castration and institution of hormone therapy. Pre-medication readings of this woman ranged from 120/80 to 170/120. Blood pressure findings recorded ten months after oophorectomy ranged constantly between 180/120 and 200/130.

#### SUMMARY AND CONCLUSIONS

The effect of the combination of castration and testosterone treatment was studied in 29 patients with breast cancer who had undergone radical mastectomy. In 22 patients, surgical castration, in 7 patients x-ray castration was performed.

After a carefully supervised 3-month course of triweekly injections of 25 mg. of testosterone, the hormone treatment was discontinued for two months, to be resumed intermittently thereafter. The dosage plan of male hormone medication is outlined. Fifteen of the 22 surgically castrated patients had axillary metastases at the time of the mastectomy. This was also the case in six of the seven patients who underwent x-ray castration.

Since initiation of this regimen from 12 to 27 months have elapsed in the individual cases. During this period of observation, four surgically castrated patients developed new manifestations of carcinoma. In one of the patients treated by x-ray castration, metastases in the chest wall and in the supraclavicular lymph-nodes developed during the hormone treatment. These five patients all had axillary involvement at the time of mastectomy. It is evident that the combination of castration and testosterone treatment does not offer an effective protection against the formation of metastases in patients who have been operated on for carcinoma of the breast with axillary involvement.\*

Signs of masculinization developed in almost all patients, but proved to be of a temporary nature on reduction of the testosterone propionate dose. Not infrequently increase of libido and excessive vaginal secretion were observed. Both serum calcium and inorganic phosphorus levels were not significantly changed by the combined treatment. There seemed to occur a moderate, most likely temporary, increase in the alkaline phosphatase content of the serum. Urinary calcium excretion remained normal. No marked changes in blood pressure were observed.

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\*Since the manuscript has been in the hands of the editor, two more of the surgically castrated patients and one other patient treated by x-ray castration developed new manifestations of carcinoma notwithstanding testosterone treatment. These developments only emphasize the conclusions mentioned.



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## THE PARATHYROIDS IN PREGNANCY

H. J. STANDER, M.D. AND R. E. AHEARN, M.D.

(New York, N. Y.)

*From the Department of Obstetrics and Gynecology, Cornell University Medical College  
and the New York Hospital*

It is generally stated that the parathyroids hypertrophy during gestation and that its normal development and progress are dependent upon the parathyroid hormone. This hormone has an influence on calcium and phosphorus metabolism. An increase of the hormone results in an increased serum calcium, decreased serum phosphorus and an increased excretion of these elements in the urine; while a hypofunction of the parathyroids brings about a decrease in serum calcium, an increase in serum phosphorus and lowered excretion of both in the urine.

During the past year we have had two remarkable cases of dysfunction of the parathyroids complicated by pregnancy; one of hypoparathyroidism and the other of hyperparathyroidism. The following is a brief description of these two cases.

### A CASE OF HYPOPARATHYROIDISM IN PREGNANCY ASSOCIATED WITH A MALFORMED INFANT

*History.* C. G. This was the first New York Hospital admission of this twenty-five year old white, registered, primigravida who was admitted because of a history of hypoparathyroidism. The last menstrual period was on July 7, 1944, making the expected date of confinement April 14, 1945. Her obstetrical course was uncomplicated save for hypoparathyroidism. The history of her illness follows.

In May of 1941 the patient noticed paresthesias with quivering of the face, fainting spells, and muscular stiffness. Her calcium was found to be 5.9 and the phosphorus 7.5. Treatment with calcium was of no avail. In June, 1941, she was benefited by AT 10 (dihydro-tachysterol). In June, 1942, it was found that she had developed urticaria to AT 10 after all else had been ruled out. She was started on parathyroid hormone, 4 to 90 units daily. She developed tolerance to this therapy; the effect was not prolonged and the drug was costly. In August, 1942, AT 10 was resumed with no further difficulty. In 1943 she married and was anxious to become pregnant. In January, 1944, she followed her husband in army camps. She stopped taking AT 10 with loss of consciousness during menstrual periods. She responded to intravenous calcium; her serum calcium was then 6 mgm. per cent.

On July 7, 1944, the patient had the last normal menstrual period with the expected date of confinement on April 14, 1945. In August, 1944, she had two weeks of spotting with no cramps. In February, 1945, she was seen by one of our medical consultants, who anticipated no difficulty during pregnancy as long as she was carefully regulated on AT 10. He anticipated no fetal abnormalities. When she was first seen she was being maintained on Winthrop pearls of AT 10 (hytakerol) and drops of the liquid dihydrotachysterol. As term approached her requirement became greater for the drug and she had occasional paresthesias.

*Examination.* The patient was a well developed white female with vertical grooving of the teeth and ridges on the nails. There were no lens abnormalities in the eyes. Chvostek and Trousseau signs were negative.

*Laboratory data.* The hemoglobin was 9.0 grams; white blood count, 10 000 with normal differential; hematocrit, 32. Urine examination was negative, with Sulkowitch test for calcium two-plus. At the time of admission before the onset of labor the calcium was 7.48 mgm. per cent and phosphorus 5.7. The amount of medication was increased from 10 to 15 drops of hytakerol daily and the resulting levels were in the range of 7.7 mgm. per cent for the serum calcium and 6.0 for the phosphorus.

*Course.* The patient had a spontaneous premature rupture of the membranes thirteen hours before the onset of labor. Labor lasted twenty-four hours and was terminated by an outlet forceps delivery because of a prolonged second stage. The third stage lasted eight minutes and was uncomplicated; the blood loss was 100 cc.

The infant presented many abnormal features. It was a female weighing 2690 grams. Both ears were deformed; the nose was flattened, a large tag of epithelial tissue was present at the left angle of the mouth; the mouth was enlarged to the left; the right thumb was absent and the fingers of the right hand were deformed; the right radius was absent. There were no other abnormalities and the infant survived in good condition.

At the time of delivery the serum calcium of the cord was 9.67 mgm. per cent, whereas that of the mother was 7.6 mgm. per cent. By the time of discharge she was well; the calcium and phosphorus serum levels had returned to more normal levels although she required less medication. Her post partum course was afebrile.

*Comment.* We were at a loss to explain the abnormalities in the infant, although we felt that very possibly there was some relationship between the mother's disease and the deformities of the child. Our experience with this type of case was not large enough to draw any conclusions.

In a review of the literature, 240 cases and three of their own, Anderson and Musselman found no fetal abnormalities, although they encountered several cases of spontaneous abortions, premature infants, deadborns, postpartum deaths, and sterility. There were twelve cases with AT 10 treatment antepartum with no abnormalities of the fetus.

*Diagnosis.* The diagnosis is difficult because so many pregnant women have paresthesias and cramps in the legs resembling tetany. We often resort to treatment of these cases in the clinic with calcium and viosterol. It has been reported that the Chvostek sign is positive in 75 per cent of pregnant women; cathode closing contraction is present in 80 per cent. This is augmented by hyperventilation at the time of delivery. The worst trouble comes at the fourth month with increased estrogen production. Estrogen has a depressing action on the serum calcium. Possibly the placenta may produce a calcium depressing substance. With rapid fetal growth starting then, there is calcium deposition in the infants' skeletons with deprivation of the mothers'.

Values of calcium below 8.5 mgm. per cent and phosphorus above 4.5 are abnormal. With variations from these figures one is apt to get hyperirritability of the peripheral neuromuscular system and various forms of muscle spasm. Breathing may become difficult with laryngeal spasm, and tonic convulsive seizures may occur. One must rule out eclampsia, hysteria, epilepsy, hypoglycemia, meningitis and brain tumors.

*Follow-up.* The patient was seen in a follow-up visit on February 4, 1946. At that time she was very anxious to become pregnant again. She related that her child was doing fairly well at another hospital and was gaining weight. A definite diagnosis of congenital heart disease had been made on the infant, but a mediastinal mass that had been obvious since birth was still undiagnosed.

The patient herself has been gainfully employed as a stenographer. Her weight has been stable at 130 pounds. She is distressed, however, over the fact that she is now taking more AT 10 than ever before; 25 to 30 drops of hytakerol a day, in contrast to 8 drops before the pregnancy and the 15 drops a day taken during gestation. She is taking 3 to 4 teaspoons of calcium lactate a day now, which is more than she took previously. Especially at the time of her periods does she become nervous, faint, and notice muscular twitching; then the medication has to be increased. When seen in the clinic she was menstruating and a Chvostek's sign could be readily elicited. She is being regulated and followed closely by

her own physician who is attempting to maintain her serum calcium at about 10 mgm. per cent and the phosphorus at 4. When the blood was last examined the calcium and phosphorus were at this level.

It is difficult to advise this patient as to the proper course to follow in regard to future pregnancies. From the work of Murphy in Philadelphia it is apparent that a mother who has one deformed infant runs a much greater risk of giving birth to another abnormal child. It is problematical whether the abnormality of the mother's calcium metabolism is directly responsible for the deformities of the fetus.

It has been shown that in dogs, with the parathyroid removed, tetany ensues with pregnancy; although it is not immediately fatal to the mother, it often results in death and abortion of the fetus. In the rat, with the parathyroid removed, there is reduced fertility, reduced numbers in the litter, prolonged labor, high maternal and fetal mortality and tetany at term.

*Treatment.* A convulsion may be averted or aborted by intravenous calcium gluconate 10 to 20 cc. of 10 per cent solution. Parathyroid extract may be parenterally given; but it is costly, the duration of action is short and tolerance develops. In the chronic case, calcium lactate, 25 to 30 grams in water, may be given daily, in addition to a low phosphorus diet, omitting cheese, meat, glandular tissue, milk and egg yolk. More fruit, vegetables, carbohydrates and fats should be eaten. Vitamin D is effective, but it is not so efficient in promoting phosphorus excretion. AT 10, derived from irradiated ergosterol by which tachysterol is converted to dihydrotachysterol, was first described by Holtz in 1933. The preparation used is an 0.5 per cent solution in oil. An initial dose of 3 to 10 cc. is given daily and the dosage then adjusted according to the calcium and phosphorus serum levels, symptomatology and the urinary calcium excretion, as determined by Sulkowitch test. The specific gravity of the urine must be watched. The patient needs more medication in pregnancy and during periods. Symptoms of excess are polyuria, thirst, abdominal cramps, tinnitus, vertigo and calcium metastases in the kidneys.

*Congenital malformations.* With deficient diets, Warkany of Cincinnati consistently found skeletal abnormalities developed which were preventable by treatment with pigs' liver. Skeletal abnormalities, like rickets in the fetus, developed in mothers whose diets were deficient in vitamin D. Pigs deficient in vitamin A developed abnormalities of the eyes, ears, missing limbs and hare lips. Rats deficient in vitamin A developed abnormalities of the eyes; skeletal abnormalities developed with lack of riboflavin in rats.

It is interesting to note that Thomas reported a case in which tetany appeared in six successive pregnancies, disappearing in the periods between pregnancies.

#### A CASE OF HYPERPARATHYROIDISM IN PREGNANCY

*History.* K. B. This was the first admission of a twenty-five year old white, married, primigravida whose present illness may be described as follows. Symptomatically she was well until three months before admission when she fell and strained her left knee. It failed to respond to the usual treatment and she was seen in the orthopedic clinic of our

hospital where an x-ray revealed a cystic appearance of the femur and patella. During that period of time she had noticed polydipsia, polyuria, increased muscular weakness and the necessity for more frequent dental repairs. A radiographic examination of the skull, spine and long bones revealed generalized osteoporosis with coarsened trabecular structure of the bones and numerous cystic areas. A flat plate of the abdomen revealed calcification within both kidneys. A radiographic impression of hyperparathyroidism with diffuse bone involvement, generalized osteitis fibrosis cystica of Von Recklinghausen, was borne out by the finding of a serum calcium level of 20.6 and serum phosphorus of 3.6 mgm. per cent.

Her last menstrual period was on October 14, 1945, making her ten weeks pregnant at the time of admission. Her case was further complicated by a history of hypertension. In 1943 she had been refused admission to the Woman's Army Corps because of a blood pressure of 178 systolic. During the study, her blood pressure stabilized at 140 systolic and 80 diastolic while at bed rest, but was found to be very labile. The rest of her physical examination was fairly unremarkable save for a nonpitting edematous appearance of the skin, especially of the face. The eye grounds were normal.

Further laboratory studies showed no excessive glucose or albumin in the urine. Daily calcium excretion varied from 500 mgm., on a high calcium diet, to 350 mgm. a day, on a low calcium intake. The urine concentrated to 1013 and diluted to 1009. The phenolsulphonephthalein excretion was 58 per cent in two hours. The urea clearance test averaged 49 per cent on two tests. The urine culture was positive for staphylococcus albus. The hemoglobin was 11 grams; red blood count, 3.5 million; white blood count, 9,300 with an unremarkable differential. The Mazzini test was negative. The average values for the blood chemistries were as follows: blood urea nitrogen 15 mgm. per cent, blood sugar 90 mgm. per cent,  $\text{CO}_2$  combining power 51 volumes per cent, cholesterol 278 mgm., serum protein 6.8 mgm., calcium 15.7 to 20.6 mgm., phosphorus 3.6 to 2.6, serum phosphatase 7.6, sodium 307 mgm. per cent, and potassium 18.8 mgm. per cent. The chest plate was negative; an electrocardiogram depicted a left axis deviation, but was otherwise normal.

*Course.* It was our impression that, because of the border-line blood pressure, poor renal function and the inevitable further drain on maternal calcium stores which would result in the later months of pregnancy, the patient should have an interruption of the pregnancy. Even if a successful parathyroidectomy were carried out, the repair of the lesions already present would be very slow, some taking years to return to normal. We also considered the possible deleterious effect on the fetus.

A therapeutic abortion was therefore carried out. Particular caution was exerted at the time of the operation so that no pathological fractures would result from anesthesia excitement. Avertin basal anesthesia was employed effectively.

After her therapeutic abortion she was well save for occasional pains in the limbs. X-rays taken at that time revealed an interval increase in the amount of cystic areas involving the distal end of the femur. She was transferred to the surgical service where operative exploration of the neck was carried out. A parathyroid adenoma was removed, measuring approximately one and one-half centimeters in diameter. Subsequently, her calcium and phosphorus levels returned to normal limits. A long period of rest is to be anticipated and a slow convalescence must proceed before she may be regarded safe from pathological fracture.

#### DISCUSSION

The decision to terminate the pregnancy in a case of hyperparathyroidism reported by Spingarn and Geist was determined largely by the presence of extensive fibrocystic disease of the maternal skeleton associated with a negative calcium balance. This indication of moderately severe hyperparathyroidism led to the conclusion that it would be harmful to allow the patient to continue to bear



the added metabolic burden of gravidity. The continuance of pregnancy with the patient in positive calcium balance was believed inadvisable in view of the tendency for diets rich in calcium, phosphorus and vitamin D to accelerate the development of serious renal complications of hyperparathyroidism. Likewise, exploration for a parathyroid tumor during pregnancy was not attempted because it was felt that even if the offending agent were found, its removal would endanger both mother and fetus by precipitating severe tetany. Thus, a brief consideration of the possible effects of coexisting hyperparathyroidism and pregnancy would serve to justify abortion as the logical therapeutic measure. In regard to the infant, insufficient calcium and phosphorus because of a mineral deficiency in the mother would tend to impair the calcification of the fetal bones producing a condition like fetal rickets in osteomalacia. On the other hand, should the fetus be able to divert the maternal mineral stores from the path of excretion characteristic of hyperparathyroidism, the increased availability of bone forming minerals might lead to excessive calcification of the developing bones.

That pregnancy may be an etiologic factor in some cases of hyperparathyroidism has been suggested by some. The evidence to date is not very convincing on this point.

#### SUMMARY

1. Hypoparathyroidism results in decreased serum calcium, increased serum phosphorus and lowered excretion of these in the urine.
2. A case of hypoparathyroidism in pregnancy, associated with a malformed infant, is presented in some detail.
3. Hyperparathyroidism results in increased serum calcium, decreased serum phosphorus and increased excretion of these elements in the urine.
4. A case of hyperparathyroidism in pregnancy is described, including treatment during and following gestation.
5. The effect of pregnancy on these conditions is discussed.

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## GYNECOGRAPHY

IRVING F. STEIN, M.D., F.A.C.S.

(Chicago, Ill.)

The contribution of Dr. I. C. Rubin (1) in establishing patency of the Fallopian tubes with gas in cases of sterility marked an epochal advance in gynecologic progress. Acceptance of this fundamental procedure was rapid, both here and abroad, and it was soon to become an essential step in every sterility investigation. The simplicity, safety, and practicability of the Rubin test has brought both credit and fame to its originator. Every student of medicine is now familiar with the Rubin patency test, and every gynecologist appreciates its value.

Soon after publication of Rubin's method, Peterson (2) adapted it to a broader field of diagnosis than was intended by its originator. He extended and prolonged the test in order to induce sufficient pneumoperitoneum to enable him to clearly visualize the intrapelvic organs on the x-ray film, the gas serving as a contrast medium to the denser pelvic viscera. Pneumoroentgenography was thus accomplished; to this diagnostic procedure, we have applied the term "gynecography" (3). A litre of carbon dioxide gas is introduced into the peritoneal cavity and the patient is placed in a prone, partial knee-chest posture so that the gas separates the pelvic organs from the intestines, permitting the pelvic viscera to be clearly visualized by x-rays. In addition, then, to proving permeability of the oviducts, Peterson also demonstrated a means of recording the size, shape, density and relationships of the uterus and ovaries on x-ray films. This technique was further broadened, in cases where transuterine inflation was contra-indicated or inadvisable, by inducing *transabdominal* pneumoperitoneum. These procedures provided a practical means of recording the intrapelvic status on the x-ray film comparable to chest plates, or gall-bladder and stomach films in their respective fields.

Peterson's evaluation and recommendations of twenty-five years ago are still valid and should be reconsidered in the interests of accurate diagnosis by both the gynecologist and roentgenologist. They may be reprinted here to advantage:

"The pneumoperitoneal roentgen-ray examination is a great aid to accurate obstetric and gynecologic diagnosis.

In suitable cases and with the proper technic, gas inflation is free from danger.

The apparatus for gas inflation and pelvic roentgenography is simple and inexpensive and can be used in any obstetric or gynecologic examining room.

The method should not be used in cases of acute pelvic inflammation or when disturbances of circulation may arise from sudden abdominal distention.

Since carbon dioxide gas is absorbed within half an hour, it is preferable to oxygen gas for inflation, since the latter gas may not be absorbed for days.

Whenever possible, the transuterine should be chosen in preference to the

transperitoneal route for the introduction of the gas because of the valuable information it furnishes regarding the permeability of the Fallopian tubes.

Excessive quantities of gas cause great pain. Experience has shown that for the ordinary case, 1000 cc. of gas will cause only moderate discomfort and is sufficient for good roentgenograms.

With the proper position (partial knee-chest with tilted table) and the rays directed perpendicularly to the plate in the axis of the pelvis, the pelvic organs are clearly shown by roentgenography.

Experience with pneumoperitoneal pelvic roentgenography will enable the observer to diagnosticate with great accuracy the pathologic changes in the pelvic organs.

There is every indication that pregnancy can be diagnosticated as early as the sixth week by pneumoperitoneal roentgenography.

Bimanual pelvic examination and pelvic pneumoperitoneal roentgenography are not antagonistic diagnostic methods. Each is valuable and their value is enhanced if they be used in conjunction, each acting as a check upon the other."

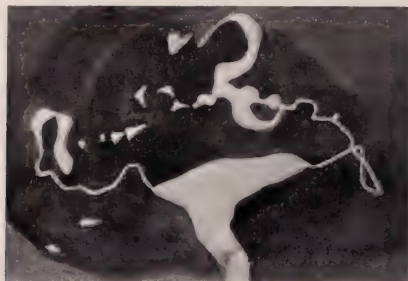
Soon after Peterson's publication, we at Michael Reese Hospital began to utilize pelvic pneumoperitoneum as a diagnostic aid and were soon convinced of its great value. We have continued to use it in selected cases for over twenty years and have made a number of contributions in medical literature attesting to its worth (4). In 1926, after Forestier (5) suggested the use of lipiodol as an opaque contrast medium in the genital tract as a complement to the Rubin test, we added this to our technique of *complete gynecography*, i.e.: both gaseous and opaque media to obtain more complete visualization (6) by the combined use of pelvic pneumoperitoneum and hysterosalpingography. By this means we were often able to obtain the maximum information about the uterus, ovaries, and tubes that was possible short of exploratory laparotomy, and more than could be gained from any other single diagnostic method.

An x-ray examination of the female pelvis may not be essential for the diagnosis of most of the common lesions found on routine examination, but for a *complete survey of the pelvis, gynecography is prerequisite*. This is well illustrated in the investigation of sterility patients where a clear picture of the uterus and ovaries is as essential as a demonstration of the permeability of the Fallopian tubes. Frequently lesions are revealed which were wholly unsuspected after bimanual examination.

Hysterosalpingography is one form of *partial gynecography* (fig. 1a) in which the size and shape of the uterine cavity and the patency or obstruction of one or both tubes may be recorded on the roentgenogram by utilizing opaque medium. The wide acceptance of this modification of Rubin's test probably resulted from the graphic permanent record of tubal patency or obstruction. Pneumoroentgenography, the other form of *partial gynecography* (fig. 1b), is obtained by x-ray of the pelvis after inducing pneumoperitoneum; either by the transuterine (patency test) or transabdominal route. It effectively reveals the uterus, ovaries and tubes on the film so that the normal and altered organs can be distinguished readily. The latter (pneumoroentgenography) is the more

informative method of the two. When the two methods are combined, i.e., adding opaque medium after the pneumoperitoneum has been induced, *complete gynecography* is obtained (fig. 2).

The sole reliance upon bimanual palpation and inspection for the routine



a



b

FIG. 1. a. Hysterosalpingography (Partial Gynecography). Sterility. Normal uterine cavity and patent tubes. Intraperitoneal spill of opaque medium.

b. Pneumeroentgenography. (Partial Gynecography). Secondary Sterility, 4 years. Inconclusive Aschheim Zondek. Pregnancy, 7 weeks. Note wide isthmus portion of uterus and enlarged, slightly asymmetrical corpus. (Transabdominal inflation of abdomen).

pelvic diagnosis is perhaps the greatest indictment of the gynecologist. Although such routine is adequate for the detection of ordinary gross lesions, there is hardly a gynecologist of experience who has not been chagrined because of an incorrect diagnosis at one time or other. When a specialist in gynecology

performs a laparotomy for ectopic and discovers a normal intra-uterine pregnancy, it is embarrassing to him; insofar as the patient is concerned, it might be construed as negligence if the doctor has failed to utilize all diagnostic methods available to him before resorting to surgery. Ovarian lesions are often misdiagnosed, overlooked or confused after the usual vagino-abdominal or recto-abdominal palpation, but these can be clearly differentiated by gynecography, especially when the lesions are relatively small. In view of these and other diagnostic errors made by even the most expert, it is incredible that x-ray diagnosis has not had more general acceptance. Can this be due to a mass conceit within the specialty, or can blame be laid at the door of those of us who have pursued the method, but have failed to impress our colleagues? We have exhibited the films at appropriate meetings and have published a number of articles on technique and clinical application (6 and 7), all of which were enthusiastically received. Nevertheless, many leading clinics and schools have failed to add gynecography to their diagnostic armamentarium.

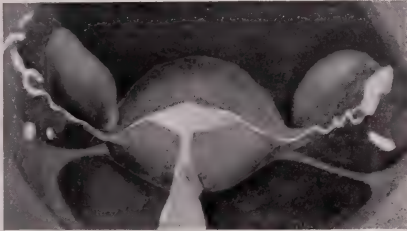


FIG. 2. Complete gynecography (Methods a and b combined). Sterility. Normal uterine and ovarian contours. Uterine cavity and tubes filled with opaque medium. Intraperitoneal spill. Normal genital status.

Just as the internist found after years of omitting chest films that much valuable diagnostic information was afforded by x-ray, so the gynecologist must come eventually to the same conclusions concerning gynecography. The technique of gynecography is not involved and should be included in the courses of gynecology offered by the medical schools. It is inconceivable that it is omitted from some of the leading diagnostic clinics in this country which utilize x-ray findings in other fields extensively. Occasional erroneous diagnoses in these clinics might be obviated if gynecography were employed. The operating room is not the place in which to establish a correct diagnosis in controversial cases.

In order to avoid repetition of previously published material, I have selected for this contribution a small group of cases chiefly to illustrate differences in opinion held by two or more physicians in which gynecography proved valuable in arriving at the correct diagnosis.



*Case 1. History.* F. M., aged 36, single, first consulted me on April 1, 1946, because of pain in both lower quadrants. Pain alternated from sharp to dull, there was no radiation and it had been present at intervals for one year. She had complained of backaches for ten years. There was some urinary frequency and occasional incontinence. Menstruation began at 12 years, was regular, of the 28 to 30 day type, of 5 to 6 days duration, the flow being profuse the first 3 days. The pain was exaggerated 5 to 7 days prior to onset and there was dysmenorrhea on the 1st day. The last menstrual period was March 17, 1946, was more profuse than usual and was accompanied by clots. Past history revealed that she was being treated for spastic colitis. She had had an appendectomy 24 years previously and was operated on for anal fistula 7 years ago. A diagnosis of ovarian tumor had been made by another gynecologist who had already reserved a hospital bed in contemplation of surgery.

*Examination.* General physical examination was essentially negative; the hymen was intact. Recto-abdominal examination gave the impression of a slightly enlarged uterus. There was tenderness and apparent fixation on the left side. However, due to rigidity and lack of cooperation of the patient, the adnexae were not clearly palpable. The impression was that of small intramural fibroids, endometriosis, and possible pelvic adhesions. In order to clarify the diagnosis and to settle the difference in opinion which existed, partial



Fig. 3. Pneumoroentgenography. Transabdominal inflation. Normal uterus, ovaries and fallopian tubes clearly visualized. Ovarian tumor ruled out.

gynecography (transabdominal pneumoperitoneum) was performed, the films revealing *normal uterus and adnexae and no evidence of intrapelvic tumor* (fig. 3). The patient was somewhat confused by this diagnosis but the demonstration of the roentgenogram convinced her that surgery was not indicated.

In the absence of demonstrable pelvic lesions, it was decided that the patient's symptoms could be attributed either to her spastic colon or to some psychogenic factor. Therefore, she was referred to her internist.

*Case 2. History.* (October 25, 1943). D. H., aged 30; married 4 years; gravid 0. This patient came for an opinion after another gynecologist had advised that she be operated upon for a cystic ovary. Menses began at 10 years, 28-30 day type, 7 days duration, profuse for 3 to 4 days, with some pain and occasional clots. She complained of dyspareunia, with pain especially on the left side of the pelvis. She also complained of profuse leucorrhea associated with itching and burning. Examination revealed a well developed young woman with marked hirsutism of the masculine type. General physical examination was otherwise negative. The labia minora were edematous and there was some chafing and excoriation of the inner surface of the thighs. Speculum examination revealed a yellow, bubbly, malodorous discharge. Both the vagina and cervix were reddened, and the uterus and adnexae were difficult to evaluate because of the extreme sensitiveness of the inflamed

vagina. A fresh smear of the discharge revealed trichomonas vaginalis and an excess of pus cells. After two months of treatment, the discharge subsided and smears were negative. Re-examination at this time revealed that the left ovary was cystic and very tender. Complete gynecography was carried out to classify the apparent ovarian swelling and to determine the cause of sterility. Her last normal menstrual period was February 25th and the date of Gynecography was March 22, 1944. Patency test revealed apparently closed tubes as the manometric pressure rose to 200 mm. Hg without clinical evidence of intraperitoneal escape. Therefore, one litre of carbon dioxide was introduced transabdominally and subsequently 5 cc. of opaque medium (lipiodol) was instilled through the author's self-retaining cannula. X-ray films (fig. 4) revealed a uterus twice the normal size, containing three nodular shadows which were interpreted as small subserous fibroids, and an enlarged, irregular uterine cavity, partly filled with gas and outlined by opaque medium which extended beyond the usual triangular shadow. Both ovaries were also somewhat enlarged.

*Course.* Although the patient's last menstrual period was February 25, less than one month before the test, pregnancy was suspected from the appearance of the uterus on the x-ray film. Subsequent events proved that this was so and the patient carried to term and delivered a healthy child. The fibroids which appeared on the x-ray grew larger during

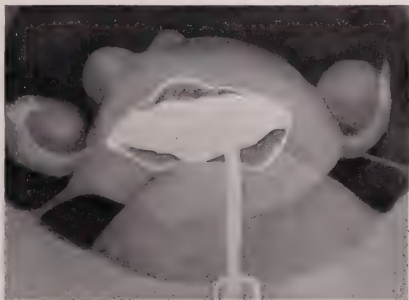


FIG. 4. Complete gynecography. Uterus enlarged. Three round irregularities on surface (fibroids). Irregular and enlarged uterine cavity outlined and partially filled with contrast medium. (Pregnancy.)

pregnancy but underwent involution with the uterus during the puerperium, and, at last examination, were not palpable.

*Comment.* Gynecography in this case was the means of diagnosing an early pregnancy in a woman with a history of four years' sterility before the first menstrual period had been missed. At the same time, an unnecessary laparotomy was obviated. Had pregnancy been suspected, transuterine methods would have been omitted; diagnoses in these cases are usually obtained by transabdominal pneumoperitoneum. No harm resulted, however, from the intrauterine instrumentation.

*Case 3. History.* S. G., aged 27, divorced, was examined on October 1, 1940, because of metrorrhagia and dysmenorrhea of 1½ years duration, and a profuse, yellow, malodorous discharge. Her menses were always irregular and lasted 7 to 8 days, the first four of which were profuse with severe clots and pain. She also complained of severe premenstrual tension. Her last menstrual period was August 27, 1940.

Past history revealed that peritonitis had complicated a D. & C. 1½ years previously. Postoperatively, smears revealed a gonorrhea which had been overlooked previously. Subsequently she had had cervical cauterization and D. & C. at both a large eastern clinic and also in Chicago without benefit. In the absence of palpable intrapelvic findings, it was concluded by the various consultants that her bleeding and pain were psychogenic in origin. She had received psychotherapy for six months in the East and was at present undergoing psychoanalysis.

*Examination* revealed a thin, nervous white female, with large breasts, the upper one-half of which were especially thick and tender. The uterus was small, erect and firm; the right adnexa were negative to palpation; the left ovary felt somewhat cystic, soft and tender. The cervix was smooth and the vagina contained some liquid and clotted blood.

*Course.* In view of the history of previous gonorrheal peritonitis, it was our opinion that there must be some intrapelvic cause for the bleeding. The findings on palpation were insufficient to account for the symptoms so x-ray was ordered. We omitted the use of opaque medium in this instance in order to prevent a flare-up of the old salpingitis or the inception of a pelvic abscess. (Cases of this sort have been reported in the literature (8 and 9).) Gynecography (transabdominal pneumoperitoneum) revealed: the uterus was smaller than normal; the left ovary was globular and approximately twice the normal size; the



FIG. 5. Pneumeroentgenography. Transabdominal inflation. Small uterus. Cystic left ovary. Tortuous club-shaped tube on right. (Left tube not completely visualized.) Bilateral hematosalpinx and lutein cyst of left ovary.

right ovary was smaller and traversing it was a somewhat cylindrical shadow which we interpreted as an enlarged Fallopian tube, either greatly thickened or containing fluid (fig. 5). A diagnosis of chronic salpingitis and left cystic ovary was made. At laparotomy, both tubes were found closed at the fimbriated ends; the right was swollen and contained dark, bloody fluid. They were soft, doughy, and of the consistency of the intestines, hence not previously identified by palpation. Both ovaries were covered with fibrous adhesions and the left ovary contained a corpus luteum cyst.

A right salpingectomy, left salpingostomy, left ovarian resection and lysis of adhesions were performed. The appendix which was adherent to the right adnexa, was also removed. Pathologic diagnosis: Chronic salpingitis with hematosalpinx, corpus luteum cyst of ovary; chronic peri-appendicitis.

*Recovery* was satisfactory. Menses became regular and normal. Dysmenorrhea, however, recurred. On November 19, 1940, a Rubin test revealed that the left tube was patent. Subsequent investigation of the vaginal discharge revealed budding yeast cells and occasional mycelial threads.

*Comment.* In this case, the patient was treated for about 1½ years for uterine bleeding and discharge, but no complete diagnosis had been made. Repeated

cauterization and curettage in the hands of several specialists failed to relieve the symptoms. In each instance, there was no palpable intrapelvic lesion found responsible for the bleeding and pain; hence it was considered psychogenic in origin and psychotherapy had been instituted. It was only when gynecography was utilized and the enlarged right tube was visualized, that the etiologic factor was demonstrated. On the basis of the x-ray findings, laparotomy was performed which revealed hematosalpinx as shown on the film. After surgical treatment, the abnormal bleeding subsided.

*Case 4. History.* (December 9, 1932) E. P., aged 27; married 13 months, gravid 0. This patient came for an opinion regarding sterility. She was under the care of a competent gynecologist who had examined a condom specimen and declared it satisfactory; he had also performed a Rubin test five days previously, and obtained a pneumograph after transuterine pneumoperitoneum. He had advised D. & C. because of uterine hypoplasia and an amenorrhea of six months' duration. A vaginal pessary was inserted to correct a retroversion. Inquiry revealed that the patient had irregular menses beginning at the age of 12 and that she now had an amenorrhea for the past 6 months. However, on August 11



FIG. 6. Pneumoroentgenography. Transuterine inflation. (Patency test.) Uterus enlarged. Uterine cavity enlarged and irregular (CO<sub>2</sub> in uterine cavity as contrast medium.) Tubes and ovaries normal. Pregnancy.

(4 months ago) there had been a scant flow and on December 1, she had spotted slightly. There were no subjective symptoms of pregnancy.

*Examination* revealed that her breasts were enlarged, the Montgomery follicles were hypertrophied and the areolae puffy. There was a suggestion of Chadwick's sign and the uterus, which was held in place by a vaginal pessary, was found to be slightly enlarged and soft. The adnexae were negative. The cervix was soft and bluish in color and there was a small amount of brownish discharge.

*Course.* A presumptive diagnosis of pregnancy was made and the first physician was contacted for permission to examine and interpret the pelvic pneumogram which he had obtained. The films (fig. 6) confirmed the diagnosis of early pregnancy, showing a definitely enlarged uterus with increase in transverse width of the isthmus (as described by Peterson). In addition, it showed an irregularly shaped and enlarged uterine cavity, the carbon dioxide gas acting as an adequate contrast medium. The right ovary was slightly larger than the left and suggested a cystic corpus luteum.

After consultation with the patient's physician and discussion of the x-ray findings, the contemplated D. & C. was abandoned. The patient carried to term and delivered a healthy child on August 27, 1933. In the absence of gynecography, an unintentional abortion would have been performed.

*Case 5. History.* (August 11, 1933) R. O., aged 36; married 16 years; gravid 3. She had a history of regular menstruation but the last menstrual period, July 18, 1931, was 10 days late. The flow was normal for 3 days, stopped for one day and she was spotting daily for 10 days. Because of cramps, she consulted a doctor at a summer resort where she was vacationing; he diagnosed ptomaine poisoning. Ergot was prescribed for the persistent but mild bleeding. Four days ago, she passed some small clots which appeared to relieve her pain.

*Examination* revealed a healthy, well built woman who did not appear to be acutely ill. General physical examination was negative. Pelvic examination revealed an erect uterus of normal size; the cervix was closed and rather soft. A doughy, tender mass was palpated in the left adnexa and tubal pregnancy was suspected. Due to the previous diagnosis of a G-I disturbance, the patient and her husband were somewhat confused by the discrepancy in the two opinions rendered. An x-ray examination was suggested and a transabdominal pneumoperitoneum was performed. The films (fig. 7) revealed a normal sized uterus; in the region of the left adnexa there was a funnel-shaped, dense shadow with the apex toward

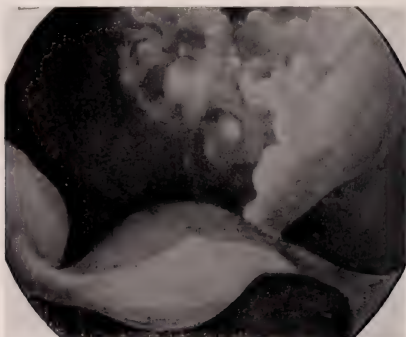


FIG. 7. Pneumoroentgenography. Transabdominal inflation. Normal uterus and right adnexa. Left cone-shaped, dense shadow with cloud-like opacity above. Left tubal pregnancy with intraperitoneal hemorrhage.

the uterine fundus. At the distal end, a cloud-like, flocculent, larger shadow was present. The right adnexa were entirely normal. The pneumoroentgenogram corroborated the diagnosis of tubal pregnancy.

*Course.* At laparotomy, there was a tubal pregnancy which had ruptured and a quantity of free blood present in the peritoneal cavity. The ovum was adherent to the ovary and to the bowel. The left adnexa were removed; the right tube and ovary were inspected, found to be normal and left intact.

Microscopic examination revealed an endometrioma of the tube with degenerated decidual cells in addition to the tubal pregnancy.

*Comment.* We have found partial gynecography (transabdominal pneumoperitoneum) to be of diagnostic value in a selected group of tubal pregnancies (10). As in the case described above, it was a means of settling a difference of opinion. In some of our cases of unruptured tubal pregnancy where diagnosis was extremely difficult, it has proved a means of corroborating a probable diagnosis.



*Case 6. History.* (April 26, 1946) A. K., aged 24; gravid 0; married 4 years, no contraception used. Present complaints were amenorrhea for two months, nausea and sensitiveness of breasts. A diagnosis of pregnancy had been made elsewhere. Irregularity of menses had been present until she had received some medication for weight reduction. Her periods were then every 28 days. She said that she had lost 22 pounds in the past six months under treatment. In the past 2 months, she had received pituitary medication.

*Examination.* It was found that the patient was short and somewhat obese, with a thick, fat abdominal wall. Weight was 129½ pounds, blood pressure, 156 systolic 80 diastolic; pulse, 120. She was visibly disturbed by the examination. The breasts appeared somewhat full and were sensitive but showed none of the signs typical of pregnancy. The uterus was small, erect and firm; the left adnexa were negative. On the right there was a soft, tender, globular swelling which appeared cystic. The cervix was firm and there was no discharge. Because of the previous diagnosis of pregnancy, and in view of the above findings, transabdominal pneumoperitoneum was performed. The pneumoroentgenogram (fig. 8) corroborated the diagnosis of cystic right ovary; it was interpreted as a lutein cyst.



FIG. 8. Pneumoroentgenography. Transabdominal inflation. Small uterus. Cystic right ovary. Lutein cyst.

The patient was observed and on May 4, 1946 she menstruated. The cyst disappeared spontaneously.

*Comment.* It is commonly known that lutein cyst of the ovary may simulate both an intrauterine and a tubal pregnancy and that frequently the diagnosis is in controversy. In gynecography, we have a means of differentiation which, as illustrated above, is of inestimable value.

*Case 7. History.* E. W., aged 25; married 3 years; gravid 0. Referred by a colleague in Milwaukee on November 5, 1945 for confirmation of his diagnosis. Menstruation began at 12 years; 30 to 35 days, 5 to 6 days duration, with occasional periods of amenorrhea. She was amenorrheic for the past five years and had a slight gain in weight. She complained of sterility, dyspareunia, and absence of orgasm. Physical examination was negative except for slight obesity. The pelvic organs were apparently normal on examination. The ovaries, however, were difficult to palpate and their size not evaluated. The referring physician had performed a diagnostic curettage in February of 1945 but no tissue was ob-

tained. The B.M.R. ranged from minus 18 per cent to plus 20 per cent under thyroid therapy. She had received various forms of hormonal treatment without benefit. The patient was very desirous of becoming pregnant and was referred for diagnostic gynecography and an opinion concerning the advisability of ovarian wedge resection for bilateral polycystic ovaries.

Transabdominal pneumoperitoneum (fig. 9) revealed marked hypoplasia of the uterus and ovaries, thus ruling out the presumptive diagnosis of bilateral polycystic ovaries. In a patient who presented a syndrome suggestive of polycystic ovaries, had gynecography not been available, the physician would have felt justified in performing a laparotomy. In this case, the x-ray diagnosis was the basis for obviating unnecessary surgery.

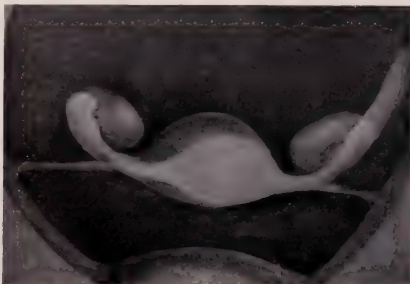


FIG. 9. Pneumoroentgenography. Transabdominal inflation. Small uterus and ovaries. Normal Fallopian tubes. Hypoplasia of uterus and ovaries. Polycystic ovaries ruled out.

#### COMMENT

Gynecography is a valuable diagnostic aid in gynecology. It is indicated in any case where the diagnosis is uncertain or obscure with the usual methods. It furthermore is useful in differentiating normal from abnormal or altered pelvic viscera. It is of particular value in obtaining a complete survey of the pelvis in cases of sterility; as shown above, it is a valuable means of settling differences in opinion. It is a safe and simple procedure. Whether to choose partial or complete gynecography is a matter of individual preference and judgment. Partial gynecography, utilizing pneumoperitoneum (fig. 1b) is our method of choice for the majority of cases. It is especially valuable where the size of the uterus or ovaries is concerned. Normal viscera, adhesions, early uterine pregnancy, tubal pregnancy, small ovarian cysts and tumors, polycystic ovaries, hypoplasia, the presence or absence of uterus, and fibroids of moderate size are readily differentiated by this means.

Questions of developmental anomalies of the uterus, such as septate bicornuate, or intrauterine lesions are best demonstrated by the second method of partial gynecography: hysterosalpingography (fig. 1a). The recording of tubal obstruction or of intraperitoneal spill is obtained by this method.

When complete information is desired about organ contours, size, shape,

relationship, and also of cavities and lumens, then complete gynecography is indicated. In the study of sterility, when complete information is desired, complete gynecography is of greatest value.

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## THE GYNECOLOGIC ASPECT OF HEADACHES

ERWIN O. STRASSMANN, M.D.

(Houston, Texas)

*From the Department of Gynecology, Baylor University College of Medicine*

Three undesirable companions follow women through life. Sometimes they appear single, sometimes combined. They are backache, constipation and headache. This unpleasant triad seems to be typical for the human female.

*Backache* is a penalty women pay for walking on their hind legs instead of on all four extremities. The primary arrangement of the genital organs provides for their leaning anteriorly toward the abdominal wall. The upright position, standing as well as sitting, changes the direction of the abdominal pressure. Any additional force or weakness of the supporting ligaments can result in retrodisplacement of the entire tract, mainly the uterus, with subsequent swelling and descent. Backache is the result.

*Constipation* is the penalty women pay for irregular eating, elimination habits and especially for insufficient physical activities. It is their widely emphasized but wrong conception that domestic activities inside the house are as good as outdoor physical exercises.

*Headache* finally is the penalty women pay for the privilege of preparing for conception every month. It is this monthly up and down cycle, the preparation for pregnancy and the events following the elimination of the unfertilized ovum, which disrupts the stability of almost every system in the female and leads among other symptoms to the very outstanding one, headache.

There are three types of headache which are typical for women, the neurogenic, the hormonogenic and the psychogenic. In making this division, it should be clearly understood that all three of them are closely knit together in their action as well as in their results. It is, however, necessary to induce a more or less artificial grouping according to the prevailing mechanism.

As an example for the neurogenic type of headache, I would like to mention the occipital "pain in the neck" which is so often found in combination with backache. In this instance the seat of the ailment is the uterosacral ligaments. Here we find a thickening of the posterior parametrium, the tissues which contain the peripheral nerves and the Frankenhaeuser ganglion. These structures run from the isthmus of the uterus upwards and posteriorly, hugging the rectum on either side to the sacrum. They are the main support of the uterus. Any pressure from above will put these ligaments under strain. Any chronic infection of the cervix may lead to swelling, thickening and final shrinking of the uterosacral ligaments. The pain associated with this parametritis posterior is primarily felt as backache. But for some unknown reason, it secondarily leads frequently to headache, which is located in the back of the head and toward the neck. Occasionally this type of occipital headache is the only symptom the patient may have. The preferable method of treatment is conservative, and consists of interal and external application of wet and dry heat, dehydrating tampons, cauterization, conization of the cervix and rest periods during the day. Moreover, the shrinkage and swelling of the uterosacral ligaments narrows the

lumen through which the rectum passes. Constipation results—thus this condition, which is the most frequent ailment I encounter in my practice, is a classical example of the combination of all the above named female complaints, backache, constipation and headache. This unfortunate fact is often overlooked and even unknown in some gynecologic circles.

While the neurogenic type of headache in the female is usually based on mechanical or local conditions, the second and most important group may be traced to endocrine disturbances.

The *hormonogenic* type of headache begins with the menarche, follows the patient through some thirty years of menstrual life and disappears after the menopause. It is strictly connected with the low tide of ovarian hormones and appears therefore most frequently just before or during the first few days of menstruation. In patients with a constant insufficient hormone level the headache may appear over longer periods, at almost any time of the cycle. They may be light and hardly disturbing, they may be severe and disabling. The worst form is the migrainous headache with nausea, vomiting and visual disturbances. The cause of this headache may be found in a periodic lack of estrogenic hormones which leads to an imbalance of other endocrine glands, especially the adrenals, pituitary and thyroid. This causes spastic neurovascular reactions in the head with subsequent headache. Most outspoken are these changes in the menopause where the neurovascular instability frequently appears in the form of spells of hypertension and the well known hot flushes. The most effective remedy for this type of headache is estrogenic hormones as prophylaxis, and ergotamine tartrate as a therapeutic measure. The corpus luteum hormone has also proved to be of value in the premenstrual phase. The pH. determination of the vagina is a good indicator of the amount of estrogens present or missing. As soon as the pH. is brought down to the normal pH. of 4.0 to 4.5 the hormonogenic type of headache will disappear.

The third and final type of headache in women is the *psychogenic* type. It is closely connected with the hormonogenic since the low tide of estrogens in the premenstrual phase and in the menopause predisposes to psychic lability and complex mental reactions. The feminine nervous instability, however, persists more or less all through life and prepares the soil for psychogenic complaints. Strong emotions, anger as well as joy, anxiety as well as pleasant anticipation, cause in certain women headache. It becomes a habit which in some instances forms a welcome excuse to avoid certain duties or responsibilities. Often it is a subconscious desire to attract attention and sympathy and to remain the center of interest.

I have found that the psychogenic type of headache is mostly present in asthenic women with flabby tissues, long slender appearance, narrow shoulders and low blood pressure, while it is comparatively rare in pycnic women with fat tissues, short stubby figures, broad shoulders and a tendency to higher blood pressure.

Psychogenic headache like other psychogenic ailments can only be accepted as present after all physical causes have been eliminated and after the background, surroundings, constitution and character have been carefully investigated.



## PULMONARY SARCOIDOSIS: ACUTE ONSET

M. TASCHMAN, M.D.

(*New York, N. Y.*)

Sarcoid disease, described originally by Boeck as an affection of the skin, has by reason of its many visceral manifestations, come to be recognized as a generalized or constitutional disease in which the skin involvement is only one of its many manifestations. Jungling directed attention to characteristic bone changes in addition to skin manifestations, and Schaumann stressed its constitutional character with emphasis on the lymphatic and blood-forming organs. Its manifestations may be few or many and vary in degree in the same patient from time to time. It may simultaneously involve the lungs, liver, spleen, lymph nodes, bones, eyes, or only a few of these structures at any given time. The clinical picture observed at any one period may portray only a single phase of the entire disease process.

Sarcoidosis is essentially chronic in character and shows a tendency toward retrogression. As many cases show widespread distribution of the lesion, it is fair to assume that at some period in its development, the disease has been more or less acute, especially since dissemination occurs throughout the body. Although this disease is uncommon, the acute phase of the onset with fever, constitutional reaction and rapid dissemination into many of the viscera, is seldom encountered and correctly diagnosed.

The typical case of the text book classification is unusual; the atypical variety is the one more commonly encountered. When limited to the visceral organs, as the lungs, only a chance x-ray may reveal pathological changes difficult to diagnose correctly unless accompanied by other symptoms, such as lymph node enlargement. In the presence of fever, sarcoidosis may easily be mistaken for Hodgkin's disease or tuberculosis.

Enlargement of the lymph nodes is almost invariably present in sarcoidosis. The mediastinal and tracheo-bronchial lymph nodes may be so massive as to resemble some type of lymphoblastoma or neoplasm. Like the adenopathy, the lungs are frequently involved in the disease process. Usually there are no pulmonary symptoms of consequence, and few, if any, physical signs.

The x-ray findings vary in distribution, amount of involvement, and morphological characteristics. The lesions may be sharply nodular or confluent and difficult to differentiate from tuberculosis of the nodular or fibrotic type. Involvement of the mid-portions and bases of the lungs is most common; clear apices help to distinguish it from miliary tuberculosis of the chronic hematogenous type. Fine, linear fibrosis in the bases, in the region of the diaphragm, is more common in sarcoid than in tuberculosis. I have seen the diffuse nodular type confused with silicosis. As resolution occurs, more or less fibrosis becomes manifest, and if pronounced, may result in disturbed pulmonary and later cardiac function.

The disease is usually benign, and patients present few subjective complaints despite many widespread pathological changes. When bone changes occur skin lesions are often present as well. The bone changes as sharply delineated rarefactions are found in less than half the cases. They usually appear in the fingers and toes, more commonly in the Negro race, and are quite characteristic. The long bones are infrequently involved. Affected fingers and toes may present fusiform swellings, often leading to deformity. The bone lesions in time regress as do manifestations in other parts of the body. The liver and spleen are at times moderately enlarged. A very large spleen may be mistaken for Banti's disease or tuberculosis. The uveo-parotid syndrome persisting for some time, as in the case described below, should always arouse suspicion of sarcoidosis.

The Mantoux tuberculin test is usually negative, as in this case, but a positive test does not exclude it. Some observers have recorded a positive Mantoux test more frequently than a negative one. A negative Mantoux test is of importance in differential diagnosis with tuberculosis which closely resembles sarcoidosis in the x-ray. In most cases, however, the diagnosis must rest on the findings of a lymph node biopsy. Difficulty in diagnosis arises when tuberculosis and sarcoidosis coexist. Though sarcoidosis may be followed by tuberculosis in the course of years, I have never encountered a case of tuberculosis in which sarcoidosis developed at a later date.

The typical pathological lesion in sarcoidosis consists of masses of epithelioid cells which often contain giant cells with no evidence of necrosis. When necrosis is present, suspicion should be directed toward the presence of tuberculosis.

There is such close resemblance in some of the clinical manifestations of sarcoidosis to tuberculosis and in the distribution of the lesions, that a relation between the two has been entertained by many workers. One patient observed by me over a period of years, beginning with typical skin lesions, ultimately developed cavities in the lungs and a positive sputum. Sarcoid resembles tuberculosis more closely than any other disease; its true etiology is not definitely known. It is specific in that the histological structure, regardless of the organ involved, is always characteristic. It is essentially a chronic disease although subject to exacerbation. It is reasonable to assume that an acute phase is present when the dissemination takes place. It is of long duration, often lasting twenty or more years. It is frequently benign in character and shows a tendency to spontaneous healing.

Some patients afflicted with this disease ultimately succumb to tuberculosis. The reason for this is not clear. Many observers have attempted to establish an etiological relation between the two, but what this relation may be, if there be one, is not known. In this city, sarcoidosis exhibits a predilection for the Negro race, and tuberculosis as an ultimate complication is seen more frequently in this race than in the white. In this connection it must be remembered that despite the drop in tuberculosis mortality in recent years, the relative proportion of four to one in the two races, still prevails.

Active pulmonary tuberculosis, previously absent, not infrequently is en-

countered following childbirth. In this connection it is interesting to note that the case of acute sarcoidosis recorded here, followed childbirth by only thirty-six hours.

An increase in the serum albumin and globulin, with an increase in blood alkaline phosphatase is sometimes found. Leucopenia also may be present.

#### CASE REPORT

*History.* A woman, colored, aged 23 years, was admitted to the obstetric service of Sydenham Hospital, at term in active labor, gravida two, para one. Her previous history was negative. On admission, physical examination was entirely negative. Blood pressure was 114 systolic and 76 diastolic.

*Course.* She was delivered spontaneously of a living female infant, the placenta was delivered spontaneously and intact. Bleeding was slight, the uterus was firm and the general condition was good.

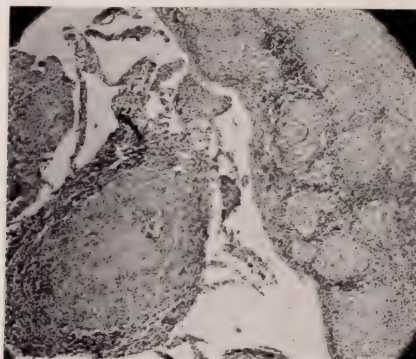


FIG. 1

Thirty-six hours following delivery, her temperature rose to 100.6°F. and over the next day rose to 102°F. No obstetrical complications were discovered to explain the fever. Physical examination was negative. Nine days following admission, dry rales were heard in the right chest. Fourteen days following admission, a chest x-ray revealed a mass in the superior mediastinum with an increase in the pulmonary markings "suggestive of Hodgkin's disease." Sixteen days after admission, a medical consultation revealed "marked conjunctivitis in both eyes; lymph nodes were palpable on the left side of the neck". A diagnosis of lymphoblastoma or substernal thyroid with pneumonia, was suggested, and the patient was transferred to the medical service. Penicillin, 2,000,000 units, and sulfonamide drugs, 12 grams, failed to influence the fever. At this time a foul vaginal discharge was noted.

Twenty days after admission the patient was seen by me in consultation, and at this time, in addition to the injection in both eyes, bilateral parotitis was noted and a bilateral cervical adenopathy. The liver was palpable three fingers below the free border and the spleen was just palpable. A diagnosis of sarcoidosis was considered and a subsequent biopsy of a cervical lymph node revealed "Boeck's sarcoid." A Mantoux tuberculin test was negative.

Her temperature fluctuated irregularly, with peaks of 102° and 103°F., gradually fell to 100°F. and then rose irregularly to 101°F. and still reached 100°F. on the fifty-fourth day after admission and two days before discharge from the hospital. On the 22nd day post partum the ocular manifestations had cleared.

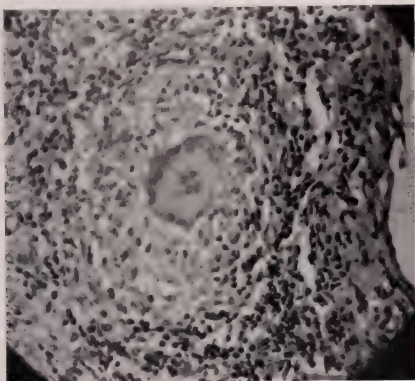
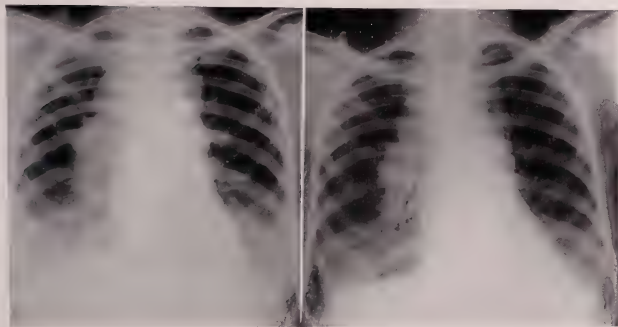


FIG. 2



A

B

FIG. 3

On the 36th day, a cervical lymph node was removed. This revealed the capsule was not clearly defined. The consistency was firm and the cut surface pinkish. The structure was distorted and the greater part of the lymphoid tissue was replaced by large, oval cells with large vesicular nuclei. Their protoplasmic outline was not always well defined. They formed small and large follicular masses, bordered by the remaining lymphatic tissue. A great number of unusually large giant cells were present. Their nuclei were not always at

the periphery; some appeared to contain basophilic exclusion bodies. No caseation or fibrosis was noted (figs. 1 and 2).

The urinalysis revealed a trace of albumin and 10 to 12 white blood cells. Blood culture was sterile. The hemoglobin was 75 per cent; red blood cells, 3,900,000; white blood cells, 5,400; polys 52 per cent of which 8 per cent were band forms. On another occasion the polynuclear cells were 67 per cent of which 12 per cent were band forms. The lymphocytes varied from 23 to 41 per cent. The monocytes varied from 3 to 7 per cent and the eosinophiles from 0 to 3 per cent. The Kahn reaction was negative. The Kline was two plus. The Mazzini was plus minus to two plus. The serum albumin was 3.4, globulin 2.8 gm. The alkaline phosphatase was 3.49 units (Bodansky), calcium 10.3 and phosphorus 4.5. There was no absolute increase in the total serum protein or in the relation between globulin and albumin and no increase in the alkaline phosphatase. The urethral smears and cultures were negative for gonococci. A chest x-ray film on January 14, 1946 showed a mass in the superior mediastinum with bilateral invasion of lung structure (fig. 3a). A chest film on January 30, 1946 showed recession of the mass in the superior mediastinum (fig. 3b).

#### SUMMARY

1. The acute onset of a case of generalized sarcoidosis with pulmonary involvement is recorded in which a febrile reaction persisted almost to the day of discharge, 54 days after admission, despite remission in the adenopathy, parotitis, eye symptoms, size of liver and spleen and the extent of chest involvement.

2. The occurrence of an acute onset of sarcoidosis in a Negress previously perfectly well, only thirty-six hours following childbirth, makes this record unique, and to my knowledge this is the first reported case of its kind.



# ROENTGENOGRAPHY AND ROENTGENOMETRY OF THE PELVIS

HERBERT THOMS, M.D.

(*New Haven, Connecticut*)

*From the Department of Obstetrics and Gynecology, Yale University School of Medicine*

The title of this paper should suggest that roentgenographic methods applied to the bony pelvis as an aid to obstetrics should serve two functions, one of which depicts the morphological character of the pelvis through roentgenography and the other which gives dimensional information through roentgenometry. Since the advent of roentgen technics to this field it is probable that too much emphasis has been placed upon the latter at the expense of the former. This is understandable when we consider that for many years the chief approach to the problem of pelvic adequacy was through pelvimetry, expressed in external pelvic diameters and obtained through palpatory methods. When roentgen technics became available, investigators seemed for the most part to have one objective in view, and that was to develop precision methods solely for the purpose of determining internal pelvic diameters and, in particular, those of the pelvic inlet. While some of the methods so developed have shown great ingenuity, many are so complicated that they are not practical for ordinary use. Furthermore, so much emphasis has been placed by some observers on matters of precision that the primary purpose of the procedures seems to have been largely overlooked. Because of this fact, the author in 1943 (1) was led to observe the following: "In consideration of any precision methods of roentgen pelvimetry, we should not forget just exactly what they mean. They simply represent the relationships of the bones of the pelvis to each other at the moment the roentgenogram was made. The obstetrician in evaluating such exact information nevertheless must realize that, not only does pregnancy itself influence these relationships, but the 'positioning' of the patient incident to the taking of the roentgenogram also may exert a certain influence. Studies of the influence of pregnancy on the pelvic articulations are well established, and the effect of posture to cause changes in pelvic relationships is also well known. It is true that such influences have but minor effects, but they are present nevertheless. Precision methods of roentgenometry, therefore, may be accurate as far as a single roentgenogram is concerned, but they must be evaluated clinically to be essentially useful. It seems reasonable to conclude that any dimension of the bony pelvic canal which is accurate to 0.5 cm. should be satisfactory and clinically useful."

The attempt by some investigators to reduce childbearing to a matter of dimensional relationships has resulted in failure because they have overlooked the fact that successful labor is dependent upon far more than the suitable adaptability of the fetus to the bony birth canal. This failure to develop methods which would mathematically plot the course of labor seems to have led to a certain disappointment among some obstetricians and roentgenologists with the result that the true value of roentgen methods in obstetrics has been to some extent mini-

mized by those who should be better informed. A more correct position is that taken by Dippel who in 1939 (2) stated: "It may be argued that there are so many factors in labor, namely, the size of the baby and the character of the uterine contractions, that an approximation is enough. We do not agree with this viewpoint. The very fact that these other factors are difficult to evaluate accurately makes it all the more important, in cases of contracted pelvis, that we should have as precise information as possible concerning the one factor that we can measure with precision."

The facts of the matter are that all essential information that is desired concerning the size and shape of the bony pelvis can be made available today by the use of roentgen and palpatory technics, but it is important to remember that the information so obtained must be properly evaluated by those who have had experience in clinical obstetrics. The obstetrician, therefore, must have in mind not only what the bony pelvis looks like but he should know something of the so-called "normal" variations of the structure and their influence upon the course of labor. We should again remind those working in the field of roentgenology that, if methods of pelvimetry are complicated and their interpretation thereby largely in the hands of the roentgenologist, the usefulness of the information will be limited. Unless films are to be viewed and evaluated by the obstetrician and he alone is to be responsible for the solution of his clinical problems, conflicts will arise which will tend to destroy the usefulness of procedures which can be of valuable aid in obstetrics.

A survey for determining the adequacy of the bony pelvis for child-bearing should include both roentgen and palpatory procedures. These should be carried out early in pregnancy for, if abnormalities are present, this knowledge is useful and may necessitate further study at or near term to determine fetal pelvic relationships as they then exist. Some have advocated waiting to apply such roentgen procedures at a later date; that is, at the eighth month or at term. There are certain objections to this. At the eighth month the fetal pelvic relationships may not represent those at a later date and the attempt to take films just at term is subject to the unreliability of the time of term pregnancy.

A practical and adequate survey of the bony pelvis should include two roentgenograms showing inlet and lateral aspects of the pelvis and should include palpation and mensuration of the outlet in the region of the pelvic arch. The inlet roentgenogram made at a 36 in. target-film distance presents a view which looks directly through the pelvis at a right angle to the plane of the inlet. The lateral film presents a view from a right angle to the lateral pelvic aspect. Both of these films are made at the same target-film distance and, therefore, the images thus produced bear a relation in size to each other, inasmuch as the distortion produced by the spread of the rays is approximately alike. This is important for, with a little experience in viewing films, one soon learns to recognize variations in size and contour of the essential parts of the pelvis. For example, in the lateral view a study of the relationship of the sacral promontory to the pelvic brim and the size and shape of the sacrosciatic notch are certainly as important as mensural information in this area. In the inlet view pelvic asymmetry and narrowing of the forepart of the pelvis are also equally important.

Certain pelvic diameters are useful for, in addition to information as to available space, they enable us to record in the prenatal history this essential data and to thus see at a glance the relation of the information to average findings. The dimensions which we have found useful for such evaluation are shown in the accompanying illustrations and roentgenograms. They are:

- For the pelvic inlet:
1. Anteroposterior diameter
  2. Transverse diameter
  3. Posterior sagittal diameter

- For the midplane:
1. Anteroposterior diameter
  2. Transverse diameter
  3. Posterior sagittal diameter

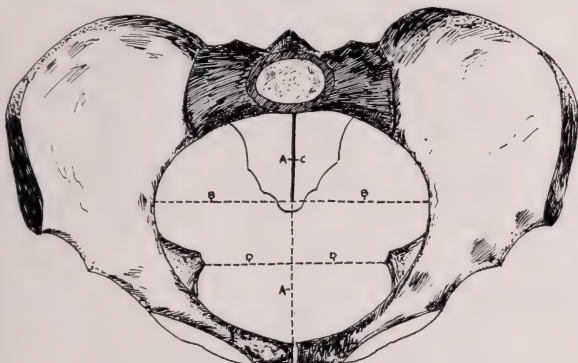


FIG. 1. The pelvic inlet

- A Anteroposterior Diameter  
 B Transverse Diameter  
 C Posterior Sagittal Diameter  
 D (Transverse Diameter of Midplane)

- For the outlet:
1. Symphysis biparietal distance
  2. Sacral biparietal distance.

These are shown in figures 1 and 2, and are superimposed in the roentgenograms 3 and 4. The correction scale is not shown in figures 3 and 4, and the technical details of the roentgen procedures will not be discussed here.

The evaluation of the adequacy of the pelvic outlet can also be carried out roentgenologically, but the results have not been uniformly good and the procedure does require an extra film. However, with the patient in the lithotomy position, direct palpation of the pelvic arch is very satisfactory and the mensuration of the symphysis-biparietal distance easily performed. Attempts to determine the intertuberal or transverse diameter of the outlet have always presented difficulties because of a lack of definite end-points. Recently Allen, of New Zealand (3), in considering this matter, made this statement in which the author

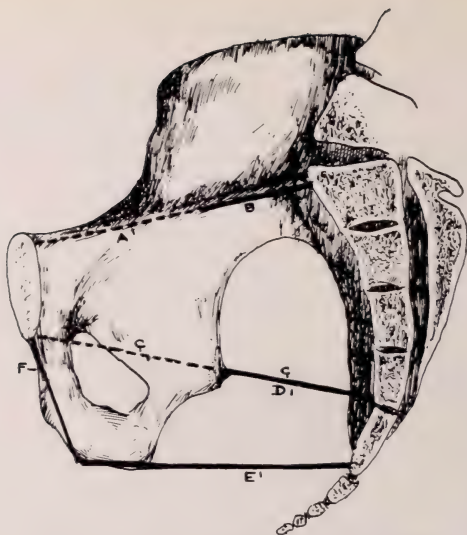


FIG. 2. Anteroposterior diameters seen in lateral aspect

- A Anteroposterior Diameter of inlet
- B Posterior Sagittal Diameter of inlet
- C Anteroposterior Diameter of Midplane
- D Posterior Sagittal Diameter of Midplane
- E Sacral-biparietal Distance
- F Symphysis-biparietal Distance



FIG. 3. Roentgenogram of pelvic inlet, Diameters shown in figure 1 (correction scale not shown)

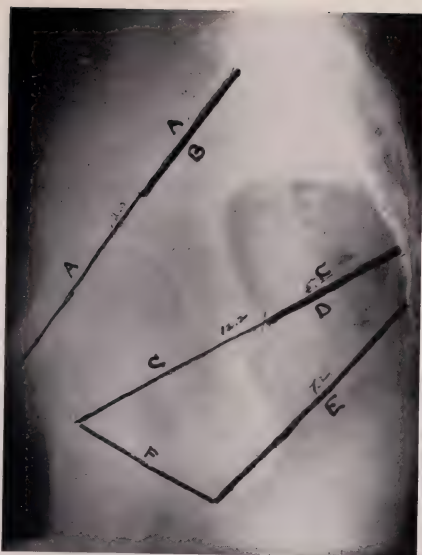


FIG. 4. Lateral roentgenogram. Diameters as shown in figure 2 (correction scale not shown)

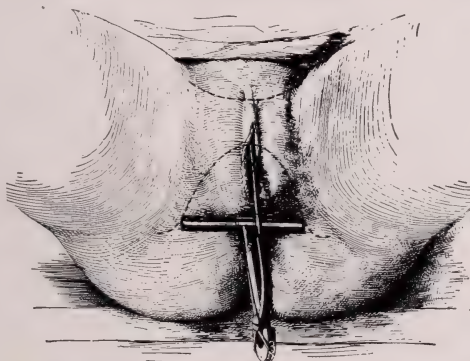


FIG. 5. The sliding cross-bar of a Thoms outlet pelvimeter has been replaced by a solid bar 9 cm. in length. After palpation of the arch this bar is brought to fit snugly between the rami. It is held in this position while the arm of the pelvimeter is placed at the lower edge of the symphysis. The symphysis biparietal distance is read from the scale.

Modified from Williams



is in ready agreement: "The bituberous diameter between the inner surfaces of the ischial tuberosities has also been discussed previously and the conclusion was then reached that this diameter could not satisfactorily be measured by any method so far described. The diameter, furthermore, is not of great importance *per se*, except in so far as it represents the free posterior end of the arch: contraction of the arch always means a reduction in the intertuberous diameter, and since the arch can be more accurately measured, there seems to be little point in measuring the bituberous." In estimating the availability of room in the pelvic arch, the question is how close to the symphysis will the occiput fit at the time of the extension of the head; or, in other words, how close will the circle represented by the suboccipital circumference fit under the symphysis. One way to evaluate this would be to see how close the diameter of this circle (biparietal diameter) can be made to fit in the pubic arch. In order to carry this out the author has modified the Thoms' outlet pelvimeter, substituting a slide crossbar for the sliding scale formerly used to measure the bituberal diameter. The average biparietal diameter has been estimated at 9.3 cms. Allowing .3 cm. for the thickness of the soft tissue overlying the sides of the arch, the crossbar is 9.0 cms. in length and represents this diameter. The determination of the symphysis-biparietal distance is simple. After palpation of the pubic arch, using both hands simultaneously, the bar is fitted as snugly as possible in the arch. It is held in this position by one hand while the other fits the movable arm to the under surface of the symphysis. The symphysis-biparietal distance is then read from the scale as shown in figure 5. Anything less than 4.5 cms. for this distance should represent adequate room under the pubic arch, except in those rare instances where the pubic rami are straight instead of arcuate. This, of course, may be determined readily by palpation. The sacrobiparietal distance may be measured either manually or from the lateral film by using the knowledge previously determined of the symphysis-biparietal distance. To recapitulate, a useful pelvic survey is here discussed and outlined. In addition to certain palpatory procedures at the pelvic outlet, two roentgenograms showing superior and lateral pelvic aspects are greatly useful in giving morphological and dimensional information. These procedures are practical and essentially simple, and their use will give a great deal of information in problems associated with cephalopelvic relationships. Their adaptability and relatively low cost should make them available to every primigravid woman wherever access may be had to x-ray service.

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## HYPERTROPHY OF THE ENDOMETRIUM

HERBERT F. TRAUT, M.D.

(*San Francisco, Calif.*)

ADDISON B. SCOVILLE, M.D.

(*Nashville, Tenn.*)

AND

ALBERTA KUDER, M.S.

(*New York, N. Y.*)

*From the Departments of Obstetrics and Gynecology of Cornell Medical School and of the University of California Medical School*

Localized hypertrophic changes in the mucosal lining of the uterus, such as endometrial polypi, are easily recognized and quite well understood; on the other hand, diffuse hypertrophy, aside from the physiological hypertrophy of the normal menstrual or pregnant cycle, is apparently not widely known and is, it seems, frequently confused with hyperplastic or adenomatous conditions of this membrane.

A review of the literature concerning the pathology of the endometrium reveals that generalized, in contradistinction to local, overgrowth of this pleomorphic membrane was probably first recognized and described by Carl Schroeder as remotely as 1877, while numerous others, notably Wyder, 1887, Uter, 1891, Semb, 1893, and Pollak, 1898, also reported studies of this condition of the endometrium. It would appear that these older views of the trophic changes in the uterine mucosa had suffered eclipse and had been discarded, along with many other contemporaneous ideas of so-called "endometritis," by the reformation of concepts occasioned by the epoch-making revelations of Heape, Hitschmann and Adler, Hartje and Robert Schroeder, bearing upon the normal variations of this tissue. Cullen in 1909 gave the first unmistakable description of hypertrophy of the uterine mucosa. This is the only account accompanied by adequate illustration, completely differentiating this condition from the normal membrane as well as from carcinoma of the endometrium. Pfeilsticker (1907), Frankl (1914), Lockyer (1918), Lynch (1922) and, finally, Deelman (1933), complete the list of writers upon the subject up to the present time. Cullen's presentation has in all probability been largely overlooked because it lies buried in an exhaustive treatise upon carcinoma of the uterus, in which he referred to it only in the chapter upon differential diagnosis. In like manner, each of the others of this more recent group of writers has referred to hypertrophy of the endometrium in connection with other uterine conditions in which they were absorbed at the moment.

There is, then, no complete and careful consideration of diffuse hypertrophy of the endometrium as such in the literature of recent time, and certainly none

of any date with illustrations which would enable the student to differentiate this condition from hyperplasia of the endometrium, with which it is not infrequently confused. It seems justifiable, therefore, to attempt to elucidate this interesting adenopathy of the uterine mucosa.

Any study of the endometrium based upon biopsy specimens secured by

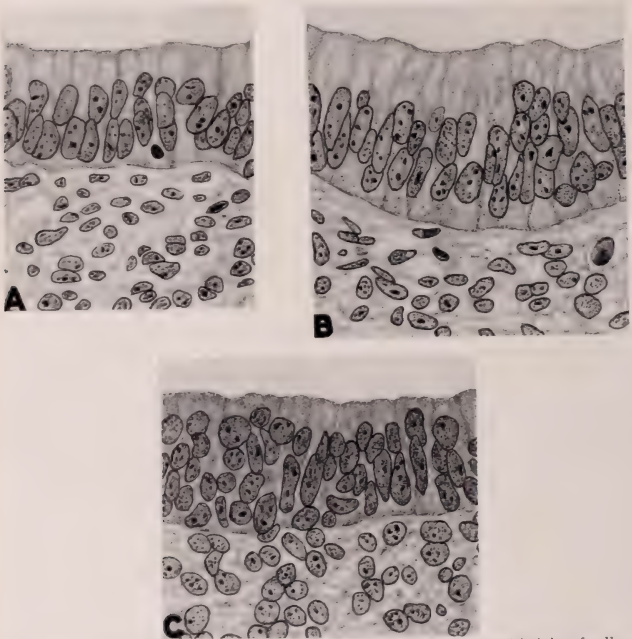


FIG. 1. a. Proliferative phase. Normal endometrium showing usual height of cells and relationship of nuclei of glandular cells and stroma.  
 b. Proliferative phase. Hypertrophic endometrium with tall cells, relative abundance of cytoplasm taking very light stain and the characteristic looseness of stroma cells.  
 c. Proliferative phase. Hyperplasia showing the relative increase in the numbers of cells with basophilic cytoplasm and nuclei and more compact stroma.

curettage of the uterus is open to criticism and error, because the tissues are traumatized, mixed with blood and must necessarily be fragmentary as well as difficult to orient. To a lesser extent, criticism may be directed by the pathologist toward endometrial material which has not been fixed promptly and before the uterine cavity is opened. The custom of opening the uterus at the operating table immediately after hysterectomy may be justified as sound practice by the

gynecologist, for it gives him an opportunity to scrutinize the endometrial surfaces and thus be more certain that carcinoma has not been overlooked. However, endometrium treated in this way quickly becomes dehydrated, the cells degenerate and many of the finer details of histological relationship are in-

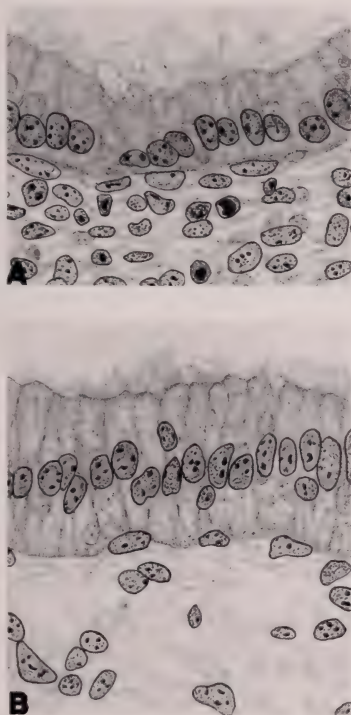


FIG. 2. a. Secretory phase. Normal secretory endometrium.  
b. Secretory phase. Hypertrophic endometrium in the secretory stage. This shows the upward displacement of the nuclei and the edema of the stroma.

evitably lost. If one is concerned with the cellular structure of the endometrium a better way is to have an assistant inject Zenker's fixing solution into the uterine cavity through the cervical canal. Then after waiting a few moments, the uterus may be opened, if desired, and when handled carefully, the delicate endometrium will then be preserved with all its normal relationships. Thus both of the ob-

jectives of the microscopist and those of the surgeon may be realized. The latter method has been the custom in our clinic and all the uterine material utilized in this study has been secured in this way. After further hardening of the uterus, blocks of tissue have been cut to represent all surfaces of the cavity and include all layers of the endometrium as well as a portion of the myometrium.

The use of the terms 'hyperplasia' and 'hypertrophy' to indicate specific disease processes is unfortunate because both terms are used more correctly



FIG. 3. Secretory phase of hypertrophic endometrium. High power.

in the general histological sense as applicable to many tissues. Hyperplasia should connote an increase in the bulk of a tissue due to multiplication of cellular elements, whereas hypertrophy means greater bulk because of an increase in the size of the individual cells constituting it. Thus, to speak of "hyperplasia of the endometrium" as a definite pathological entity cannot but be confusing. 'Cystic glandular hyperplasia' and 'metropathia hemorrhagica' are other attempts at nomenclature which, although not completely satisfactory, are desirable because they are more descriptive and have special meaning, as they



are only used to describe a definite pathological and clinical entity. The same criticism can be directed toward the use of hypertrophy of the endometrium; however, its use in this paper may be justifiable, as no definite disease syndrome

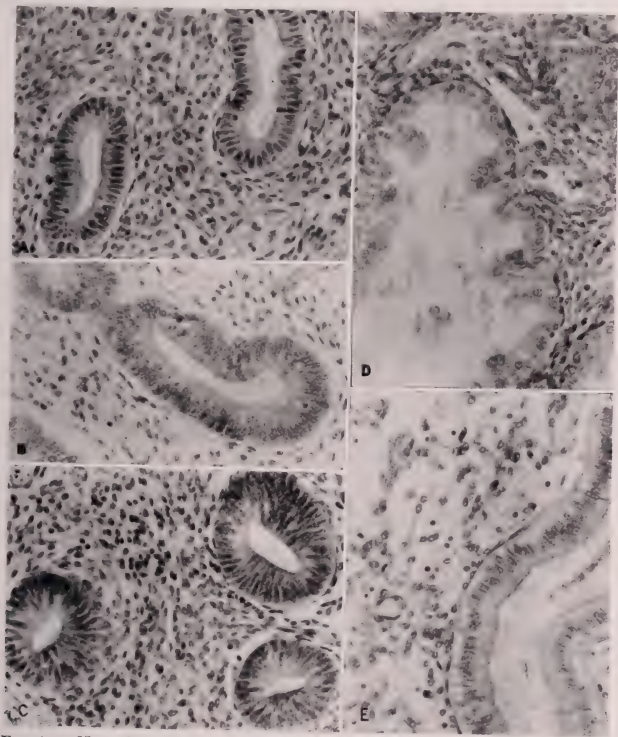


FIG. 4. a. Normal endometrium in late proliferative phase.  
b. Hypertrophic endometrium in late proliferative phase.  
c. Hyperplasia of endometrium.  
d. Normal late secretory endometrium.  
e. Hypertrophic endometrium in secretory phase.

is indicated and a generalized thickening of the membrane due to cellular enlargement is the subject of the paper.

Four hundred and forty-five uteri have been studied after fixation, as outlined above. The endometrium has been stained usually with hematoxylin and eosin,

but whenever the question of secretory activity was to be decided, Best's carmine stain for glycogen has also been made.

Four hundred and four of the uteri were myomatous, while only 41 contained no tumors. Of these, 201 were accompanied by the ovaries which were studied in correlation with the endometrium. In the total material, it was found that 30 had cystic glandular hyperplasia of the endometrium (6.6 per cent), while 176 had a definite hypertrophy (39.6 per cent). The non-myomatous uteri alone had a somewhat higher incidence of hypertrophy (25.7 per cent), and a

TABLE I  
*Phases of the hypertrophic endometrium*

	NO.	PER CENT
Proliferative.....	49	44.5
Secretory.....	54	50.0
Senile.....	6	5.5

TABLE II  
*Incidence of hypertrophy according to age*

AGE	NO. OF UTERI	HYPERTROPHIC ENDOMETRIUM	PERCENTAGE INCIDENCE
20-29	22	4	18.1
30-39	89	50	56.1
40-49	223	112	50.0
50-59	111	10	9.0
	445	176	

TABLE III  
*Location of the myoma with reference to hypertrophic endometrium*

	PER CENT
Submucous.....	35.3
Mural and Subserous.....	64.7

Hypertrophy was found in 25.7 per cent of the non-myomatous uteri studied.

lower one for cystic glandular hyperplasia (5.8 per cent). Hypertrophy of the endometrium therefore is not found only in myomatous uteri, as many have thought, for the non-myomatous uteri in this study showed an incidence of nearly 26 per cent.

Whereas cystic glandular hyperplasia was constantly associated with the follicular phase or follicular cysts of the ovary, the hypertrophy was found in both the proliferative and secretory forms and accompanied by the follicular or lutein phase of the ovary respectively.

If the morphological differences in the endometrial picture were the only

criteria for differentiation between cystic glandular hyperplasia and hypertrophy, the demonstration would be more difficult and less convincing, particularly in the borderline cases. However, the fact that hypertrophy responds to the ovarian hormones in a manner closely simulating that of the normal menstrual cycle, at once proves quite conclusively the vast difference that must lie behind their respective origins. The secretory phase of the hypertrophic membrane is most characteristic, the proliferative phase less so, although the cells of the glandular epithelium are consistently larger, while occasionally in borderline instances it is extremely difficult to decide between hyperplasia, hypertrophy and normal endometrium in this phase. However, after carefully studying the growth characteristics of the hypertrophic form, it becomes possible to differentiate them with a fair degree of accuracy.

#### HISTOLOGY OF HYPERTROPHY OF THE ENDOMETRIUM

The thickness of the endometrium is markedly increased, being often 5 mm., and sometimes even 1 or 1.5 cm., from the uterine cavity to the muscularis. The surface is apt to be wavy and sometimes approaches blunt polyp formation. It may occur in uteri which are normal in size, as well as in those in which myomata are present. In the myomatous uteri it is more apt to be found in the recesses of the cavity removed from the tumor, particularly if they be submucous. This latter observation led Pfeilsticker and Frankl to characterize the luxuriant growth as a development *ex vacuo*, because they felt that the overgrowth was explained by Walcher's theory of alternate relation and contraction of the uterine musculature which they imagined might produce a suction effect in these protected loci, followed by hyperemia, overnutrition, and hence hypertrophy of the cellular elements.

Microscopically the glands are increased in size and occasionally they are cystic, which undoubtedly has led to the confusion with cystic glandular hyperplasia. In the proliferative phase, they may be widely separated by an edematous stroma, whereas in the secretory phase, the glands are often so numerous as to leave little intervening stroma. In addition, the longitudinal contour of the glands tends to a lesser degree of tortuosity than in the normal proliferative or secretory phase.

The finger-like papillary structures so characteristic of the normal secretory endometrium are not seen, or are much blunted and are markedly reduced in number.

The glands tend to be lined by a single row of columnar cells which are much larger than normal and are sharply defined against the lumen in both the proliferative and secretory phases. These cells always appear to contain an excess of cytoplasm which is much less basophilic than normal. The nucleus is oval or round and is seldom found occupying the base of the cell, as a globule of cytoplasm tends to collect in that location. There is seldom any tendency toward multiplication of layers or "heaping up" as is so commonly seen in hyperplasia, although in the proliferative phase one sometimes sees this to a moderate degree.

The stroma cells are usually round, even in the proliferative phase, especially if edema be present, which is particularly apt to be the case at the periphery. In the deeper portions the stroma may be more compact and the cells spindle shaped. The staining reactions are quite uniformly basophilic and pale.

The vessels commonly show thin walls and over-distention, as though passive congestion were quite constant.

Differentiation between hyperplasia of the endometrium and hypertrophy in the secretory phase offers no possible obstacle in characteristic specimens. If, however, the secretory activity is early or questionable, the answer may be sought through the aid of the glycogen stain.

In the proliferative phase, however, the differences are not so striking and one may well make errors until the eye is trained to note the regularly spaced epithelium of the glands and the paucity of epithelial cells as compared with hyperplasia, in which condition they are usually markedly increased in number. Cystic glands may occur in both conditions, although they are much more characteristic of hyperplasia than of hypertrophy.

#### ETIOLOGY

It has been pointed out that hypertrophy of the endometrium is found in the non-tumorous as well as in the myomatous uterus. There is, therefore, no reason to assume a causal relationship between the tumors and this condition of the mucosa. The same conclusions are valid regarding a possible relationship between cystic glandular hyperplasia and myomata, which some have endeavored to demonstrate.

Uter (1891) was probably the first to describe hypertrophy unmistakably, although C. Schroeder had earlier given descriptions and pictures which probably were hypertrophic endometrium, and ascribed the presence of myomata as its cause. Later (1893), he indicated the cause of both myomata and hypertrophy as inflammatory in nature. Semb (1893) definitely separated its etiology from inflammation which, in his time, was the usual explanation of all unusual conditions found in the endometrium. Pollak (1898) felt that compression of thin walled veins by the tumors produced passive congestion which, in turn, was responsible for the overgrowth of the membrane by a process of overnutrition. Pfeilsticker (1907) invoked the Walcher theory, that the uterine musculature reacted to the myomatous tumors as though they were foreign bodies it was trying to expel. The alternate contraction and relaxation of the muscular viscus, he thought, produced a negative pressure or suction effect which in turn influenced the mucosa to overgrowth. Cullen (1909) frankly said, "We have absolutely no clue as to its causation." O. Frankl (1914), speaking of these changes in the endometrium, refers to them as "hyperplastic endometrium" although he could not have meant cystic hyperplasia for he says: "The mucosa is thickened and edematous and passes through a stage resembling premenstrual swelling. It is a development *ex-vacuo*." He quite evidently was in at least partial agreement with Pfeilsticker. Lockyer (1918) writes: "Like the muscu-

TABLE IV  
*Characteristics*

	CYSTIC GLANDULAR HYPERPLASIA OF THE ENDOMETRIUM	GENERALIZED ENDOMETRIAL HYPERTROPHY
Thickness	0.5 cm. to 1 cm.	0.5 cm. to 1.5 cm.
Polyp formation	++	++++
Hemorrhagic areas	++++	+
Edema	+	++++
Stroma cells	Spindle shaped, usually closely packed. Markedly basophilic—mi- toses +++	Oval to round, loosely ar- ranged. Palely basophilic—mitoses +
Blood vessels	Occasional congestion— thrombosis +	Passive congestion marked.
Glands:		
1. Number	Relatively few	Few in proliferative phase— numerous in secretory phase.
2. Tortuosity	Very moderate	More marked than hyper- plasia, but less than in normal endometrium.
3. Cyst formation	++++	++
4. Intra-lumen papillae	Scarce	Rare in proliferative phase, occasional in secretory phase.
5. Diameter	Vary markedly (smaller than normal to huge cys- tic glands	Rather marked uniformity, but usually considerably larger than normal.
Glandular Epithelium:		
1. Cells	Numerous layers, spindle nuclei, scant cytoplasm, marked basophilia.	Proliferative phase may re- semble hyperplasia, but fewer layers of cells; oval nuclei, more cytoplasm, even outline of cells against lumen, pale stain, larger cells.  Secretory phase—huge cells, outlined like board fence, much cytoplasm, clear, with round, pale staining nucleus.



TABLE IV—*Concluded*

	CYSTIC GLANDULAR HYPERPLASIA OF THE ENDOMETRIUM	GENERALIZED ENDOMETRIAL HYPERTROPHY
2. Glycogen stain Ovary	Negative Usually Graafian follicle cysts, no corpus luteum.	Positive in secretory phase. Normal ovary in follicular or corpus luteum phase.
Myometrium	Most commonly normal, or with moderate general hy- perplasia of musculature, occasionally with myo- mata.	Commonly associated with myomata, though it may also be seen in normal myometria.
Age Incidence	Two groups: (14-25 yrs. and 35-50 yrs.)	35-50 yrs. greatest incidence.
Vaginal Bleeding	Exceedingly common	Very rare and then caused probably by polypi or sub- mucous myomata.

laris, the mucosa is influenced by hyperemia which prevails in cases of myomata, and it is common to find hyperplasia and hypertrophy of the lining membrane in conjunction with that of the muscle wall. The myoma may, or may not be the exciting cause, for, as was previously stated, the uterine hyperplasia and myomatous change may both be the outcome of ovarian hyper-secretion."

Lynch (1922) says that "hypertrophy may be found when a submucous tumor is present. It rarely occurs in the subperitoneal form. Even though the uterus is elongated, the mucosa rarely hypertrophies in this class of tumors. Dilatation of the veins is frequently found, and marked edema as well."

From the foregoing brief resume of the ideas of the writers upon the subject, one concludes that there is no agreement as to the cause. The age incidence may be of significance. In interpreting this factor, however, it must be remembered that uteri are seldom removed in young women and that it is only toward the end of the child-bearing period that we relax our indications for hysterectomy. Inevitably, therefore, we have a predominance of uterine material for study after the age of thirty-five or forty years and it is not surprising that we should find a greater percentage incidence. On the contrary, the variations shown between 18 per cent in the third decade as compared to 56 and 50 per cent in the fourth and fifth respectively, together with the drop to 9 per cent in the sixth, must have significance. General senile changes of all uterine tissues probably account for the lower incidence in the sixth decade. The difference between the third on the one hand and the fourth and fifth on the other requires explanation, which unfortunately we are not in a position to give satisfactorily. It seems reasonably clear, however, that in contra-distinction to true cystic glandular hyperplasia, the cause is not hormonal in nature. At least it is impossible to ascribe it to the ovarian hormones or the lack of any of them as we

understand them today. One should bear in mind, however, the possible relationship of other hormonal factors, perhaps those of the anterior hypophysis. Certainly the fact that the condition seems to be progressive during the reproductive period and then diminishes very markedly thereafter, strongly suggests a relationship with the reproductive forces of the body. However, it appears more likely that it is a form of trophic disturbance resulting from prolonged passive congestion and excessive edema, and that in all likelihood those factors such as tumors, torsions of the uterus, and malpositions which may be associated with stasis of the lymph and blood stream are the responsible ones.

From the clinical point of view, hypertrophy of the endometrium has little or no significance in itself. It is important, however, to differentiate it from cystic glandular hyperplasia which, having great clinical importance, is often confused with it. Hypertrophy is not a common cause of abnormal endometrial bleeding when it is of the diffuse type. Localized hypertrophy or polypi, on the other hand, are frequently hemorrhagic because of necrosis of the tips of the elongated structures which have outgrown their blood supply.

#### SUMMARY

We have attempted to call attention to generalized endometrial hypertrophy, to define it and differentiate it from cystic glandular hyperplasia. Its greatest importance, outside the boundaries of pure scientific interest, lies in the fact that it is commonly confused with other conditions. It is most frequently found in women during the last half of the reproductive period and disappears with the establishment of the menopause. The most probable explanation of its origin seems to be prolonged passive congestion of the blood and lymph vessels.

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## APPLICATION OF AUTO-HEMOTHERAPY IN GYNECOLOGICAL CASES

ROBERT WALLIS, M.D.

(*New York, N. Y.*)

By auto-hemotherapy, one means the treatment of a patient by his own blood. Utilized during some forty odd years for immunization purposes as well as for desensitization, this method of treatment has been employed especially by skin specialists. With P. Abrami and J. Dalsace of Paris, I have studied its application and benefits in the treatment of gynecological disturbances and of sterility in women, for over twenty years. The following is just a short summing-up of my experience with this therapeutic measure.

The technique of auto-hemotherapy is simple. It consists of removing blood from the vein of the patient and injecting it immediately intramuscularly in the gluteal region. The best results have been obtained by removing 15 cc. each time and allowing four or five days interval before the next injection. The total amount of injections for one series of treatment is usually eight to ten injections to get both satisfactory and permanent results. We discovered that auto-hemotherapy constituted a helpful method whenever there were menstrual troubles either at puberty, or later in life at the menopause, and also in the dysmenorrhea of the adult woman between these two periods.

Auto-hemotherapy seems to act as a decongestant of the uterus and the ovaries. It is effective in metrorrhagia and menorrhagia as well. When the periods are too frequent, or too abundant, when they are painful and accompanied by clots, very often auto-hemotherapy alone is enough to stabilize the cycle, reducing the frequency of the periods or the length of the periods. At the time of the change of life, it also has an action on those functional troubles which frequently accompany the menopause such as flushes, perspiration and headaches. Very often auto-hemotherapy is insufficient but in glandular treatment seems very efficient, permitting smaller doses of thyroid, estrogen or corpus luteum, or testosterone as the case may require, to be active. Furthermore, it also seems to make the result of the glandular treatment more lasting.

Under the previously mentioned circumstances, the patients under consideration had a normal uterus and normal ovaries, but cases have also been seen in which a fibromyoma or adenomyoma was present and in which hemorrhagical symptoms were reduced by auto-hemotherapy. In any event it must be made clear that this does not constitute a cure but only an alleviation of the symptoms, whether pain or hemorrhage.

During the course of these treatments, systematically given, it was observed that in certain cases, women who were seeking to have children and could not conceive, became pregnant after the administration of auto-hemotherapy. Of course, these were cases where everything was normal locally—the cervix, the uterus, the ovaries and the tubes (tested by the Rubin test). A systematic

attempt to treat several cases of sterility where, in spite of the normal local conditions, pregnancy could not be secured, demonstrated that in fifteen per cent of these cases auto-hemotherapy was the one factor which enabled conception and the nidation of the egg to take place. This was put to experimental test on eleven mares which for two years could not become pregnant and which apparently had no focal infection of the tubes and ovaries, no local modification of the cervix or uterus. In each of these eleven cases, 50 cc. of her own blood was injected into the mare at the same time that she had the nomination. In seven cases out of eleven, after only one injection of auto-hemotherapy, the mare became pregnant. In the four cases where the results were negative, the organs were examined after autopsy and in two cases lesions of the tubes were found which had not given clinical symptoms. These results with mares were much better than those observed in women, who did not yield as high a percentage of success as the mares did. Fifty-five pregnancies were induced by this method in over seven hundred patients on whom it was attempted. In these fifty-five cases, women had attempted for months, and sometimes for years, to become pregnant, without success. In five cases, when these same women wanted to become pregnant again after a first child, auto-hemotherapy had to be given again. In all other cases, when the first pregnancy had been obtained through auto-hemotherapy, when a second or a third pregnancy was desired, it was usually obtained without auto-hemotherapy.

I have also successfully used auto-hemotherapy to decongest the uterus, tubes and ovaries in mild infections. Of course, in more serious infections, auto-hemotherapy is only a help and does not justify depriving the patient of the usual course of anti-infectious medicines and especially the new anti-biotics such as sulfa drugs, penicillin or streptomycin. The impression is left that the results were more constant, obtained in a shorter length of time, and were more permanent, when auto-hemotherapy was coupled with the anti-infectious treatment.

How does auto-hemotherapy act in these cases and in general? It was first supposed that it acted through shock, in reaction to the patient's own blood, which as soon as it leaves the vascular system and in contact with a syringe becomes a foreign protein. Indeed it is less foreign than horse serum or milk, and for that reason it induces a less violent reaction. As a matter of fact, no noticeable reaction nor pain results, no rise in temperature, nevertheless there is a reaction sufficient to produce a beneficial effect. The originators of this method (Rayant and others in Lyons) had this in mind when they decided to use the patient's own blood as a substitute for foreign proteins.

In some cases the ordinary auto-hemotherapy does not seem sufficient to induce an action. A way to increase the effects of the method consists in taking the blood of another person—hetero-hemotherapy. In three cases of sterility I was thus able to facilitate a pregnancy by injecting into the patient her husband's blood when her own blood was ineffective. Sometimes also, for instance in cases of women who have climateric flushes, headaches and perspiration, and who have been relieved by auto-hemotherapy, a second course of treatment was



ineffective. In order to make it more efficient, auto-hemotherapy was given intravenously. Fifteen cc. of the patient's blood was collected and left in contact with 2 cc. of distilled water for thirty seconds and then slowly re-injected into the same vein. The efficacy of this variety of auto-hemotherapy can only be seen by comparing two similar instances of treatment given the same patient. In twenty cases I was able to verify that this intravenous auto-hemotherapy was a more efficient method.

There are others who claim that auto-hemotherapy does not act through shock, since it is not shocking enough, but through auto-catalysis. The Russian authors, and especially A. Bogomolets, claim that blood can act as a factor to magnify immunity, or to enhance the glandular efficiency through functional stimulation, exactly in the same way and through the same auto-catalytic process as in the case of glandular transplantations.

Many things remain unknown, of course, concerning the pathogeny of these actions. Nevertheless, one can say that auto-hemotherapy constitutes a simple and efficient way of decongesting a uterus and of stabilizing the function of the ovaries. One cannot claim, of course, that this method replaces the glandular or anti-infectious treatments wherever they are required. Far from being a vicarious treatment, it constitutes a supplementary treatment which seems to help nature on its own path to recovery. It apparently magnifies the efficiency of the above-mentioned treatments and makes their results more permanent. In cases of sterility when no local symptom can account for its persistency, auto-hemotherapy constitutes one more remedy which can be tried to overcome it since, for reasons unknown, this harmless procedure appears to bring remarkable success in certain cases.

## THE TREATMENT OF CARCINOMA OF THE CERVIX COMPLICATED BY PREGNANCY

GEORGE GRAY WARD, M.D., F.A.C.S., F.R.C.O.G (Hon.)

(*New York, N. Y.*)

Carcinoma of the cervix complicated by pregnancy is a rare condition. In the Woman's Hospital during the past 19 years there were 36,274 obstetric cases, among which were 10 cases with malignancy of the cervix, 9 with carcinoma and 1 with sarcoma. This is in accord with the incidence found in other clinics, which averages 0.0321 per cent.

The occurrence of carcinoma is usually in pluriparae, rarely in primiparae. In our series however, one case was primipara. Invariably the carcinoma was present before the onset of the pregnancy.

Authorities differ as to the influence of pregnancy on the growth and malignancy of the cancer. However, I believe the greatly increased blood supply of the pregnant uterus will naturally tend to increase the rapidity of growth. The type of cancer cell, the age of the patient, and the stage of pregnancy are factors which determine the result in each individual case and account for the fact that growths develop more rapidly than others.

The presence of carcinoma in the cervix tends to cause an abortion, or premature labor, as the growth extends upward. If the growth is confined to the portio of the cervix the pregnancy may develop normally to term.

The presence of a growth in the cervix may effect the labor by interfering with normal dilatation or causing obstruction. Extensive laceration of the cervix may occur with severe hemorrhage. Sepsis is a definite danger.

The passage of the fetus through the diseased cervix crushes the tumor mass and disseminates the cancer cells through the lymphatics and blood vessels.

The diagnosis of carcinoma of the cervix may be made more difficult due to the color changes and increased softness of the tissues, and the tendency to consider bleeding due to a threatened abortion or placenta previa. Any area of induration in the softened cervical tissue of pregnancy should be regarded with suspicion. Wherever an erosion or suspicious area is present a biopsy taken with the high frequency radio-loop should be done. This technic causes the least trauma and is aseptic.

The importance of an early diagnosis is obvious. In suspected early pregnancy, if there is doubt as to the diagnosis, the Aschheim-Zondek test will be of help. The probability of a permanent cure is definitely lessened by the pregnancy, but the mortality has steadily improved since radiotherapy has been employed. Early recognition of the condition and prompt treatment by surgery and radiotherapy have improved the cure rate of mother and child.

Depending upon the development of the pregnancy the cases may be divided into two groups, early and late—those before and those after the twenty-eighth week or period of viability. In the early pregnancies the fetus will be lost due to

the treatment which is primarily in the interest of the mother. In the late pregnancies beyond the twenty-eighth week a cesarean section gives the possibility of a favorable prognosis for the child.

In our series of 10 cases of carcinoma of the cervix complicated by pregnancy, five were in the nonviable group and five were after the twenty-eighth week or viable. In the five nonviable cases one was classified as Schmitz II, or early, and in four the carcinoma had extended to the parametrium, Schmitz III. In the five viable cases two were classified as Schmitz II, and three as Schmitz III.

Of the five nonviable cases only one was salvaged for five years but died subsequently of cancer. She was aged 35 years, three months' pregnant, with a squamous cell carcinoma, Schmitz III. She had 4200 mg. hours of radium, did not abort, and one month after irradiation a supracervical hysterectomy and bilateral salpingo-oophorectomy was done. The other four nonviable cases were only irradiated. Two aborted, one in two months and died ten months later, and one in two weeks died in one year. The other two failed to abort,—one retained the fetus for thirteen months when a Wertheim operation was done, the patient dying from postoperative shock; the other had a missed abortion seven months after the irradiation and died two months later.

In the five viable cases four babies were salvaged and three mothers, one over four years, one over seventeen years, and one recent case. Four cases were treated by a Porro cesarean operation followed by radium therapy and x-ray, and one case by cesarean, radiation therapy and x-ray and panhysterectomy six months later. Brief histories of these cases follow.

#### CASE REPORT

*Case 1. (#77632)* Age 41, grav. V, para VI, 28 weeks' pregnant, squamous carcinoma of cervix, Schmitz III, Porro cesarean section, living child, radium 3938 mg. hours, deep x-ray therapy. One year later the patient developed stricture of left ureter. Sixteen months after the Porro cesarean operation she developed a beginning intestinal obstruction, lived two years, and died of recurrence of carcinoma.

*Case 2. (#78162)* Age 26, para I, pregnant full term, a polypoid growth of cervix which proved to be a sarcoma. An extraperitoneal cesarean section was done, with a living child. This was followed by 3000 mg. hours of radium and x-ray therapy, Coutard technic. Six months later a panhysterectomy and bilateral salpingo-oophorectomy was done, as a precautionary measure. Mother and child have remained well for over four years and nine months.

*Case 3. (#46898M)* Age 25, grav. V, para II, seven and one half months' pregnant; squamous cell carcinoma of the cervix, type II and III, Schmitz III, L.N. II; a Porro cesarean section and bilateral salpingo-oophorectomy was done with a living child, 4 lbs. 15 ozs. There was infiltration of the right broad ligament and right uterosacral ligament. A high amputation was done with no dissection of the bladder peritoneum. Nineteen days later 2984 mg. hours of radium was applied to the cervix stump, followed by two series of deep x-ray therapy, each of 3600 roentgens. The patient and child are alive and well over seventeen years to date.

*Case 4. (#86319)* Age 38, para III, thirty-five weeks' pregnant, squamous cell carcinoma of the cervix, type III, Schmitz III, L.N. II. A low flap cesarean and supracervical hysterectomy and bilateral salpingo-oophorectomy was done with a living child, in Hackensack, N. J. She was referred to the Woman's Hospital one month later for irradiation. She was

given 4200 mg. hours of radium to the cervix followed by deep-x-ray therapy. She survived one year and two months, dying with a general metastasis.

Case 5. (64500) Age 30, para V, 29 weeks' pregnant, squamous cell carcinoma of cervix, type II, Schmitz II, L.N. I; Porro cesarian section, baby died of prematurity. Nineteen days later 3260 mg. hours of radium was applied to the cervical stump; followed by x-ray therapy. The patient has made a good recovery but is too recent to classify.

#### TREATMENT

In all cases prompt treatment of the carcinoma is indicated. Either the radical Wertheim operation, or irradiation by radium or x-ray must be employed. The consensus of opinion today is in favor of irradiation. In the nonviable cases the death of the fetus will usually result, due to abortion or, if the fetus should continue to develop, grave injury to the child may result in malformations.

In the early pregnancies operative removal of the uterus by a radical abdominal hysterectomy has been successful in saving six out of 19 mothers, as reported by Peham and Amreich. This is done without previously evacuating the uterus and is followed by deep x-ray therapy. This method would seem only suitable for a very early carcinoma.

Irradiation is the preferable method and is usually employed in the early nonviable cases without an associated hysterectomy. This will destroy the fetus which may be delivered spontaneously, though not always. Several weeks after the death of the fetus it may have to be removed vaginally by operative procedure. This is objectionable because of the strong probability of disseminating the cancer.

In all early pregnancies, whether a radical Wertheim operation or radiation is employed, death of the fetus is inevitable, and the uterus and ovaries are removed or their function destroyed. The evacuation of the uterus as a result of irradiation means trauma to the diseased cervix with possible extension of the carcinoma. A supracervical hysterectomy in the early months will remove the fetus without disturbing the cervical region and permit the treating of the cervix as a stump carcinoma by irradiation and x-ray.

I see no reason why such a procedure is not as applicable to the early cases as those where there is a viable fetus. A supracervical amputation of the uterus is far less dangerous than a radical Wertheim operation, and the results obtained in the treatment of stump carcinoma have been as good or better in our hands, and also in other clinics, as in the ordinary cervix cases.

In cases seen after the twenty-eighth week delivery *per vaginam* is contra-indicated on account of the obstruction of a rigid nondilatable cervix and the dissemination of cancer cells which will be caused by the bruising and trauma of a forceps extraction.

The classical Porro cesarean section, removing the uterus well above the internal os, gives the best results for saving the child with the least trauma to the carcinomatous area. In two to three weeks after the operation, irradiation of the cervix and high voltage x-ray therapy is administered. Portes and de Nabias were the first to advocate this form of treatment in the viable cases.

Behney has reported a 10 per cent better percentage in his stump cases than in his total series, and Scheffey's salvage was 42.8 per cent against 20.5 per cent in his total cases. In our series at the Woman's Hospital we had an absolute survival rate of 42.8 per cent in stump cases, while our percentage for total cases was 28.5 per cent. As Behney has pointed out, the salvage of stump cases for five years in Scheffey's, Behney's and our clinic, if combined, was approximately twice that achieved with general carcinoma of the cervix in the same clinics.

The general impression has been that cancer of the stump is more difficult to treat and with less hope of success than cancer of the cervix with the corpus present. I do not believe this is so and I agree with Behney's statement that stump cancer responds to treatment in a manner similar to cases where no hysterectomy has been done and with generally better results.

A retarding factor in the development of the cancer should be expected due to the diminished circulation and lymphatic drainage caused by the castration combined with the subtotal hysterectomy.

#### COMMENT

The type of treatment to be adopted is a perplexing problem, and each case must be individualized, but in view of the results reported by others and our own experience I believe that in general, all early cases of pregnancy where viability of the child is out of the question, a high supracervical hysterectomy and bilateral salpingo-oophorectomy should be first done. This removes the fetus without trauma to the cervix, avoids the abortion or missed abortion with its danger of trauma to the cervix, sepsis and dissemination of the cancer cells. This should be followed in about two weeks with irradiation of the cervix stump and high voltage x-ray, as in the treatment of all stump carcinoma cases.

In cases in the last three months of pregnancy with a viable child, a cesarean section is indicated before irradiation of the cervix. A Porro cesarean should be done with removal of the adnexa and, as soon as possible, irradiation of the cervix stump, and high voltage x-ray should follow.

The question of irradiating the cervix before the Porro operation is done may be open to discussion. In general, irradiation of a pregnant uterus is inadvisable due to the damage to the child which may follow, even in late cases, as shown by studies of Murphy and Goldstein.

The case reported by Sir Comyns Berkeley is one in point. In August, 1914 he operated before a group of us, who were visiting in London, on a woman at term with a carcinoma of the cervix, (evidently an early one). She had been irradiated previously at the twenty-sixth week when first seen. He did a classical cesarean with a living child and at the same sitting did a radical Wertheim operation. The child had two bald patches on an otherwise hairy head, these being surely due to the action of the radium. He reported the patient and the child as alive and well, twenty years later in 1934.

In a patient who is in the sixth month of her pregnancy and who is anxious



for a child, a minimum dosage of irradiation of the cervix may be given first. This will temporarily arrest the progress of the carcinoma. When viability is attained the Porro operation is done, followed by deep x-ray therapy.

#### CONCLUSIONS

As a result of the reports of others and in the light of my own experience, I have come to the following conclusions.

1. Irradiation of the cervix by radium and high voltage x-ray is the most desirable treatment for the carcinoma of the cervix complicated by pregnancy.

2. In the nonviable cases, a supracervical hysterectomy should be done immediately, sacrificing the fetus and, as soon as recovery warrants, irradiation of the cervix stump followed by high voltage x-ray therapy should be performed. Thus trauma to the cervix in evacuating the uterus, and the danger of disseminating the cancer cells are avoided. The benefit of the retarding factor resulting from the castration is also obtained.

3. In pregnancy seen at the sixth month, where a child is anxiously desired, irradiation of the cervix may be done before the hysterectomy, in the hope of getting a living child.

4. In all viable cases a Porro cesarean section should be done first, followed by irradiation of the cervix stump and high voltage x-ray therapy.

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## RESECTION OF HYPERPLASTIC ADRENAL GLANDS FOR FEMALE PSEUDOHERMAPHRODITISM

SEYMOUR F. WILHELM, M.D.

(*New York, N. Y.*)

*From the Urological Surgical Service of the Beth Israel Hospital*

Although references to intersexuality are frequent in ancient Hebrew, Egyptian, and Grecian art and literature, it was not until comparatively recent times that the association of female pseudohermaphroditism with adrenal hyperfunction was established. The most frequent pathological finding is hyperplasia of both adrenal glands although a few cases have been reported due to adrenal cortical tumor.

Hyperfunction of the adrenal gland is accompanied by increased secretion of androgenic hormones. When this occurs in utero, the female embryo is profoundly masculinized with hypertrophy of the clitoris and malformation of the external genitalia. Determination of sex by the usual methods of physical examination is often difficult if not impossible. In such instances, exploratory laparotomy may be required.

Supplementing the investigations of Cahill and others (2, 3 and 5) with perirenal insufflation, I introduced and have continuously employed the laminographic method for the visualization of the normal and the enlarged adrenal gland (8 and 9). By means of this technic, accurate roentgenographic delineation of the normal and the hypertrophied adrenal gland has been achieved with satisfactory regularity and with minimal risk. In cases of doubtful sex, the finding of bilateral enlargement of the adrenals on the laminographic films is presumptive evidence of the presence of female internal genital organs, and thus the necessity for exploratory laparotomy may be obviated.

Vaginoscopy and hystero-salpingography has also proved helpful in determining the sex of older children and adult pseudohermaphrodites.

Adrenal hyperplasia was accompanied in our cases by an increased excretion of androgenic hormones in the urine contrary to Soffer (6), who has stated that the urinary androgen excretion is usually normal or may be slightly or moderately increased. The colorimetric assay of the urine in two of my cases showed a great elevation in the excretion of the 17-ketosteroids. Adrenal hyperplasia was demonstrated in both by laminography following perirenal insufflation, and, in one of these cases, by operation and histological examination. In this patient total excision of the left adrenal gland and extensive partial resection of the right adrenal was followed by a sharp diminution in the urinary 17-ketosteroids and was accompanied by remarkable clinical improvement.

### CASE REPORT

*History.* M. D. (Beth Israel Hospital No. 151068) a pseudohermaphrodite, aged 23 years, was referred to me by Dr. S. Boxer in November 1942. She complained of burning on urination, frequency, and occasional incontinence.

She always felt tired, had little ambition, and found it difficult to obtain or keep a job. She was brought up as a female, despite the fact that she had a fairly large phallus and



FIG. 1. Preoperative photograph March 11, 1943. Note masculine body form, absence of breast development, and high forehead.



FIG. 2. Preoperative photograph, showing hypertrophied clitoris

masculine body form and distribution of hair. She shaved daily and stated that she had no sexual desires or experiences. There was no breast development (figs. 1, 2 and 3).

Examination at this time revealed a small urogenital introitus which barely admitted the little finger. Cystoscopy and vaginoscopy showed that the urethra emptied into the

anterior wall of the vagina about 5 cm. posterior to the introitus, forming by this junction a urogenital canal. The bladder was inflamed but otherwise normal. The urine was cloudy and contained pus. The blood pressure was normal, but the urinary androgens on November 9, 1942, were markedly elevated, 145 mgs. per liter, and 252.3 mgs. per 24 hours (17 keto-steroids) (Dr. M. Biskind).

The patient had been a premature child and had spent the first year of her life in a hospital. In 1933 and 1934 she had been observed at the Lincoln and the Mount Sinai Hospitals. A summary from the latter reads, as follows: "A 14 year old patient with definite hirsutism of chin and cheek, masculine type breasts; hips not well marked; fair degree of hirsutism on legs, slight on arms, and not at all on thorax or trunk. Well marked imperforate phallus, size of a male of 12. Below this is a funnel-shaped opening through which the urine is voided. Rectal examination disclosed no evidence of a vaginal canal. Gonads could not be felt in the pelvis or in the inguinal canals. Psychometric studies revealed average intelligence. X-ray of sella turcica showed it to be somewhat small, but normal in shape. Intravenous urogram was normal."

A diagnosis of hermaphroditism with low average intelligence was made and it was decided to regard the patient as a girl. Progynon-B was administered and the patient was under observation at the Mount Sinai Hospital until 1941, with no change in her status.



FIG. 3. Preoperative photograph, showing hypertrophied clitoris and opening of urogenital sinus

The cystitis for which she consulted me promptly subsided with the administration of sulfa drug, and on March 1, 1943, the patient entered the Beth Israel Hospital for adrenal gland studies.

*Course at hospital.* Laminography following perirenal insufflation revealed marked enlargement of both adrenal glands (fig. 4). X-ray of the skull showed no abnormality. Despite some dissenting opinion, I believed that the patient was a female with excessive masculinity caused by hyperactivity of the adrenal glands.

On March 11, 1943, I explored the abdomen through a low right rectus-splitting incision, and found a small uterus, ovaries, and tubes. The uterus measured 4 x 3 x 2 cm. Both ovaries were small and soft and a biopsy was made of the right ovary. There were no testes. The laparotomy wound was closed, and through a lumbar incision the left adrenal gland was exposed extraperitoneally. It was enlarged to about 3 times the normal size and was completely excised. It weighed 21 grams. Pathological examination (Dr. A. Plaut) showed hyperplasia of the adrenal cortex and a hypoplastic ovary (figs. 5, 6 and 7).

Following operation, blood pressure levels were maintained, but convalescence was complicated by a pneumothorax and atelectasis of the left lung. The wounds healed promptly and the patient left the hospital well on the sixteenth postoperative day. Androgen determination (17-ketosteroids) by Dr. M. Biskind on that day showed 74 mgs. per liter, as compared to the preoperative figure of 145, and 138 mgs. per 24 hours, as compared

to 252.3 mgs. There was no apparent change in the hirsutism, body configuration, breast development, or clitoris. She noticed, however, for the first time a small amount of vaginal bleeding lasting 8 days.

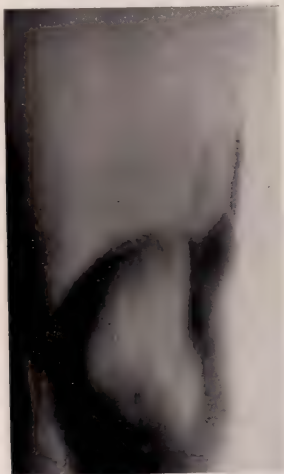


FIG. 4. Laminogram following perirenal insufflation, delineating a greatly enlarged right adrenal gland.

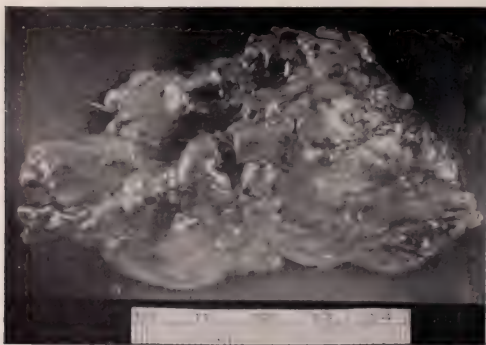


FIG. 5. Surgical specimen. Entire left hyperplastic adrenal gland

Cyclic bleeding has continued since this time. The patient was treated with diethyl stilboestrol during the spring of 1943 and during the following summer. The breasts



became larger and the nipples hypertrophied. The general body contour appeared more feminine. Androgen determination (17-keto-steroids) on September 13, 1943, showed 60 mgs. per liter, and 142.8 mgs. per 24 hours.

The patient reentered the hospital on October 4, 1943, and 3 days later I exposed the right adrenal gland through a lumbar incision. It was much enlarged and similar in appearance to the left adrenal gland. I excised the inferior third of the right adrenal gland

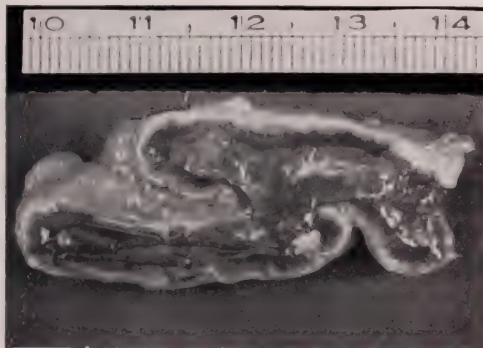


FIG. 6. Surgical specimen. Bisected left adrenal gland

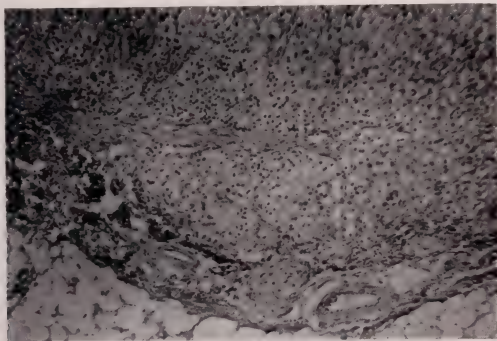


FIG. 7. Microphotograph of hyperplastic adrenal gland

and estimated that, including the adrenal tissue devitalized by clamps and by transfixion sutures, about 50 per cent of the functioning tissue of the right gland had been eliminated.

The postoperative condition was excellent, blood pressure was maintained, and the patient was out of bed with a healed wound on the ninth postoperative day. On the fourteenth postoperative day, I amputated the clitoris and did a median episiotomy, mobilizing and enlarging the vagina. The patient recovered promptly, leaving the hospital on the

tenth postoperative day. Androgen determination (17-keto-steroids) on October 30, 1943, showed 72 mgs. per liter, and 99.36 mgs. per 24 hours.



FIG. 8. Postoperative photograph (1945). Note widening of hips and development of breasts and nipples

Since leaving the hospital, the patient has been treated intermittently with estrogenic hormones by Dr. Morton Vesell. There has been a remarkable change in her physical and mental characteristics. She is now alert and active and has been doing sustained work.



FIG. 9. Postoperative photograph (1945), showing breast and nipple development



FIG. 10. Postoperative photograph (1945), showing the external genitalia

She still shaves, but now uses cosmetics and has developed a normal feminine interest in clothes. Cyclic vaginal bleeding has continued; the hips and buttocks have widened (figs. 8, 9 and 10).

The urinary androgen determination (17-keto-steroids) on September 9, 1946, showed 17.9 mgs. per liter, and 32.3 mgs. in 24 hours.

#### COMMENT

Female pseudohermaphroditism, although uncommon, is not extremely rare. I have now under observation three such patients, and Young ( 7 ) reported four, three of whom were subjected to partial resection of the adrenal glands. In one, a 5 year old girl, the result was good. In the remaining 2 patients, however, sisters aged 15 and 13½, there was no breast development or vaginal bleeding following bilateral partial adrenal resection. Broster ( 1 ) excised an entire adrenal in an adult without any striking improvement, and concluded from this that these patients should be operated before the onset of puberty. It seems likely that an insufficient amount of hyperplastic adrenal tissue has been resected by these investigators and that the situation may be analogous to the surgical treatment of hyperthyroidism before subtotal thyroidectomy was employed.

The amount of adrenal tissue necessary for the maintenance of life and health has not been determined, nor has it been possible to maintain life with adrenal cortical extract and desoxycorticosterone following total excision of both adrenals ( 4 ). In the case reported above, the entire left adrenal gland was enucleated and at least one third of the right adrenal resected. Furthermore, it is evident that in mobilizing and excising part of an adrenal gland, necrosis due to trauma, infarction, and infection, may compromise considerably more tissue than is actually cut away. On the other hand, it is likely that less hyperplastic than normal adrenal tissue is required for life maintenance.

#### SUMMARY

A case of female pseudohermaphroditism, due to bilateral hyperplasia of the adrenal glands is reported. Laminography following perirenal insufflation clearly delineated the enlargement of both adrenals, and exploratory laparotomy with biopsy of the right ovary confirmed the essential feminine constitution of the patient.

The hyperplastic left adrenal gland was completely excised and at least one third of the hyperplastic right adrenal was resected. The vagina and urethra opened into a narrow urogenital sinus requiring a plastic perineal operation. The greatly hypertrophied clitoris was amputated.

The excretion of urinary androgens (17-ketosteroids) was elevated prior to operation. Following adrenalectomy, there was a decided decline in urinary androgen excretion, which, however, still remained considerably elevated.

Striking clinical improvement occurred after the adrenal resections with the onset of cyclic vaginal bleeding, growth of the breasts, and a remarkable mental transformation. The body assumed a feminine conformation, but the excessive growth of hair was not affected. The total amount of adrenal tissue surgically removed in this patient represents, I believe, the largest amount excised in man

without fatal outcome, and the absence of deficiency symptoms indicates that the upper limit was not exceeded.

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## MELANOMA OF THE VULVA WITH REPORT OF TWO CASES

KARL M. WILSON, M.D.

(Rochester, N. Y.)

*From the Department of Obstetrics and Gynecology of the University of Rochester*

Melanoma of the vulva is a rare but extremely interesting type of tumor. Taussig, in a large series of 155 examples of vulvar malignancy, had only four of the melanotic type, three of whom died and one of the *mons veneris* who survived for seven years. A recent series of thirty examples of vulvar malignancy reported by Watson and Gusberg includes two melanomas but the results of therapy in these two cases are not stated.

The melanoma usually originates in a pre-existing pigmented mole or nevus, but this original focus may be so insignificant as to escape detection. Malignant change when it occurs is most likely to be in women over fifty years of age but it of course may on occasion occur at a much earlier age. Considering the frequency with which the common type of pigmented mole is encountered about the vulva, in a region where it is readily exposed to irritation by clothing and the wearing of protective pads, it is rather surprising that malignant change does not occur in them more often than it actually does. After malignant change has developed these tumors usually assume a high grade of malignancy and if untreated, the course is ordinarily a rapid one, with local extension of the growth, ulceration, and rapid metastasis by both the lymph and blood streams, so that a fatal outcome is the usual end result at an earlier date than is the case with the more usual forms of vulvar malignant disease.

Histologically these tumors may present the appearance suggestive of either a sarcoma or carcinoma, with the characteristic deposition in the cells of large amounts of the pigment melanin. However, whether a given tumor is to be regarded as a sarcoma or carcinoma is probably of only academic interest at the present time. In different microscopic fields of the same tumor the cell types may vary, and the same is true of the metastases. Again, while the tumor cells may be of an epitheloid type in appearance they may not be of epithelial origin. Furthermore it is interesting to note that some metastases may contain considerable numbers of pigmented cells while others contain none. Whether the histological appearance suggests sarcoma or carcinoma the grade of malignancy in either case will be high. After all the term melanoma is probably a more satisfactory one to use.

Two examples of this unusual type of tumor are herewith presented—one of which followed the usual rapid course with a fatal termination, while the other survived for several years after operation. Strangely enough these two patients presented themselves within a few weeks of each other and none have been seen in any clinic before or since.

*Case 1.* L. G., Unit No. 61303, age 67, was first admitted to the Medical Service of the Strong Memorial Hospital, May 27, 1932. She was admitted primarily on account of a

severe diabetes, known to have been present for seven years, combatted by diet and insulin, but for the past two months she had had no insulin. Two months before admission she had noticed a dark area in anterior vulva which had increased somewhat in size but which had not ulcerated nor had it caused any other symptoms. She was not aware of any pre-existing pigmented area in this region prior to the development of the present growth.

*History.* She had undergone ten normal full-term pregnancies, had an uneventful menopause eighteen years previously and diabetes was known to have been present for seven years, otherwise the past history is irrelevant. After the diabetic condition had been brought under control she was transferred to the gynecological service.

*Examination.* In addition to the known diabetes, physical examination revealed a fairly marked generalized arterio-sclerosis, but apart from the local lesion, no other findings of significance were noted. Wassermann reaction was negative and radiograph of the chest was negative. Pelvic examination revealed some relaxation of the outlet with healthy senile mucosa, while the uterus including the cervix appeared to be quite normal for a woman of this age as did the appendages.



FIG. 1

Just anterior and somewhat to the right of the clitoris was seen a rounded, protruding, deeply pigmented nodule, 1.5 cm. in diameter. Adjacent to this nodule the surrounding skin was deeply pigmented for a distance of 2 cm. from the margins of the nodule, in a somewhat irregular manner (fig. 1). There was no ulceration of the pigmented area and no inguinal or femoral glands could be felt.

*Course.* She was considered too poor an operative risk, for a complete radical operation, so it was decided to do a vulvectomy first and later remove the glands if she responded well to the first operation.

On June 13, 1932 complete vulvectomy, including removal of the clitoris was done by means of the electrocautery knife. A good closure was obtained and she made a very satisfactory recovery with excellent healing of the operative site. With this gratifying result the second stage, removal of the inguinal and femoral glands was carried out some weeks later. Recovery following this procedure was also uneventful. One femoral gland was found to be invaded by metastatic growth.

Histological examination of the vulvar tumor showed the predominating type of cell to

be a rather long, spindle-shaped type of cell most of which were deeply pigmented. At the same time other cells were seen which were not of such marked spindle shape and some more

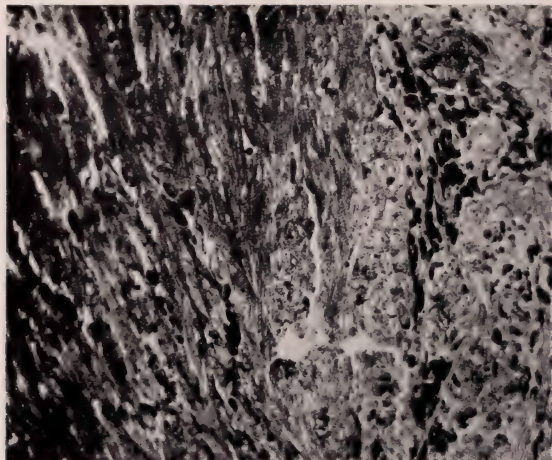


FIG. 2



FIG. 3

nearly approached the epitheloid type. Many of these were also deeply pigmented (fig. 2). The tumor was quite vascular but not unusually so. If one were attempting a differentiation, this tumor could probably be classed as being of the sarcomatous rather than car-

cinomatous type. Histological examination of the single involved femoral gland showed similar pigmented cell types.

She was very cooperative in her follow-up visits and was seen at frequent intervals for the first three years post-operatively. When seen on April 2, 1942 which was almost ten years after operation, her condition appeared to be quite satisfactory, but a month later she was admitted to the hospital in diabetic coma and died a few hours after admission—aged 77. Unfortunately no autopsy could be obtained.

*Comment.* This patient represents a ten year survival (less a month) after operation for melanoma of the vulva with a glandular metastasis. She also represents an example of the agreeable surprise one encounters from time to time in medical practice when an expected sombre prognosis fortunately proves to be erroneous.

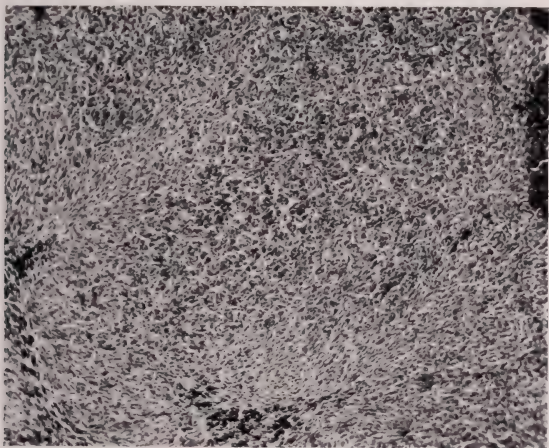


FIG. 4

*Case 2.* H. D., Unit No. 63075, age 68, was admitted to Strong Memorial Hospital on July 16, 1932 with the complaint of vaginal bleeding and growths on the vulva.

*History.* Four months previously she had noticed a small "pimple" on the external genitalia. This was painless and did not bleed so she paid no attention to it. Since that time several others appeared, increased rapidly in size and recently there had been a small amount of bleeding from one or two of them. Recently some dyspnea on exertion developed and in the past three months there had been a weight loss of 43 pounds.

The menopause occurred thirty years previously, apparently uneventful. There had been no full term pregnancies, but two had occurred which terminated prematurely, one at three months and the other at seven months. Otherwise the past history is irrelevant.

*Examination.* Revealed an elderly, markedly emaciated woman. Apart from the local genital lesions the significant findings included a small area of dullness in the right upper chest in which numerous moist rales could be heard after coughing. Radiograph of this



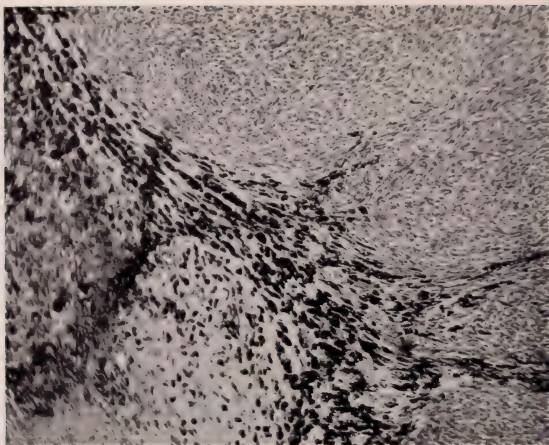


FIG. 5

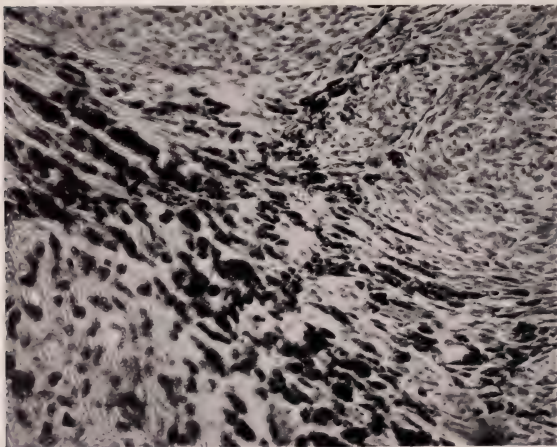


FIG. 6

region showed a small, rounded circular shadow under the third rib, and a similar smaller one on the left. They were regarded as metastatic growths in the lungs. The Wassermann examination was negative. Blood pressure was 150 systolic and 78 diastolic. Some gen-



eralized arterial sclerosis was found to be present. On both sides in the inguinal and femoral regions large masses of non-sensitive glands could be felt.

Pelvic examination revealed an extraordinary state of affairs. Multiple, darkly pigmented (nine in all) tumors were present. These were isolated one from the other and varied in size from half a centimeter to two and a half centimeters in diameter (fig. 3). The larger ones were partially pedunculated and were ulcerated superficially, bleeding on touch, but were quite painless. Bi-manual examination revealed nothing significant in the vagina, uterus or appendages.

*Course.* It was obvious that the situation was a hopeless one but as a palliative measure the individual tumors on the vulva were removed by means of the electro-cautery knife, on July 20, 1932. As a purely palliative measure, deep roentgen therapy was given to the inguinal glands.

The operative site healed satisfactorily and she was discharged from the hospital after seven days. She was seen three times after discharge, the last time on September 6, 1932, at which time her general condition was found to be deteriorating, and the shadow in the right lung was found by radiograph to be increasing in size. She died at home six weeks later, three months after she was first seen and eight months after the first growth appeared. No autopsy could be obtained.

Histological study of the tissue removed at operation showed a varying picture in different microscopic fields. Portions of the tumor consisted of solid masses of rather small, closely packed, cells. Comparatively few of these presented pigmentation (fig. 4). Adjacent to such areas were noted strands and masses of rather spindle shaped cells, which were for the most part, quite deeply pigmented. Strands of these cells were also seen to be growing into the other portions of the tumor (figs. 5 and 6). As in the tissue from Case 1, a fair degree of vascularity was noted but not to any unusual degree.

*Comment.* This patient is a fairly typical instance of an untreated malignant melanoma of the vulva with a rather rapid course, metastases to the regional lymph nodes and to the lungs occurring early in the disease, death taking place about eight months after the onset.

#### DISCUSSION

Two examples of primary malignant melanoma of the vulva are presented, one of whom survived for ten years after a complete two stage operation, while the second followed a rapid course to a fatal termination.

The second case illustrates well the rapid course which is apt to follow in patients with this type of tumor when an early diagnosis is not made and treatment not instituted. On the other hand the first case illustrates the fact that though highly malignant such tumors are not necessarily hopeless, if seen sufficiently early. However two cases are obviously of no statistical value.

Operation consisting of complete vulvectomy with removal of the regional glands in either one or two stages would appear to be the method of choice in the suitable case. In deciding the operability examination of the patient should include not only the genital exploration to determine the local extent of the growth, but also a radiograph of the chest to learn if the lungs already show metastatic lesions. If the latter are present local removal of the genital growth would obviously have only a palliative effect. Deep roentgen therapy may be used to supplement surgery but its value is doubtful and probably the effect would also be purely palliative.

Prophylaxis is of limited application, but might well include the removal of pigmented moles or naevi situated about the vulva before any malignant change occurs. Even this minor procedure should, however, be carried out with the most meticulous care, and should include excision of healthy skin for a distance of at least a centimeter on all sides of the mole or naevus. Furthermore, the incision made should include the entire thickness of the skin in order that extirpation of the mole or naevus may be complete. The greatest care should be observed to be sure that the little growth is not squeezed or otherwise traumatized. Too often these small growths are regarded of no significance, and are removed by grasping with a forceps and snipped off by scissors, only to be followed by a malignant growth at a later date, because of the incomplete removal and the traumatic irritation associated with such a procedure.

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REACTION OF THE FALLOPIAN TUBES TO INCREASED  
INTRA-UTERINE PRESSURE OF CARBON DIOXIDE  
GAS AS DETERMINED BY THE KYMOGRAPH<sup>1</sup>

THOMAS R. WILSON, M.D.,

*Fellow in Obstetrics and Gynecology,  
Mayo Foundation,*

AND

LAWRENCE M. RANDALL, M.D.,

*Section on Obstetrics and Gynecology,  
Mayo Clinic, Rochester, Minnesota*

Transuterine tubal insufflation with carbon dioxide under controlled pressure is a standard method employed primarily to test the patency of the fallopian tubes. When patency of the tubes is demonstrated, there are certain characteristic variables of the curve representing the pressure necessary to cause gas to pass through the tubes, as measured with a kymograph. In this article, some of the factors that may alter the pressure curves and the significance of the alterations will be considered.

One thousand and twenty-nine cases of infertility were reviewed. In 343 of these cases the histories and physical findings did not reveal any evidence of pathologic change or anatomic variation in the pelvic viscera. Any variation in the kymographic tracings could reasonably be ascribed to the normal or abnormal variation in physiology. In addition to the exclusion of evidence of disease by history and physical examination, the basal metabolic rate was determined, the menstrual history was reviewed and, unless the transuterine tubal insufflation was performed during the stage of proliferation (first half of the menstrual cycle), the endometrium was examined microscopically.

In 1926 Rubin (12) began to study the tubal contractions with a kymograph attached to the apparatus for transuterine insufflation. By means of the kymograph, the variations in pressure can be recorded readily. The question arises as to what is normal patency. Experience has taught that there is a variation in the amount of pressure necessary to permit the gas to escape through the normal tubes. Rubin has shown, by experiments on extirpated specimens and by a study of clinical cases in which the abdomen has been opened and the tubes exposed to view, that the initial rise in pressure in the normally patent tubes is less than 100 mm. of mercury and frequently is not more than from 40 to 60 mm. The kymogram will reveal a variation in pressure after the initial drop, as long as gas passes through the tubes. This variation is between 10 and 40 mm. of mercury. These fluctuations of pressure have been noted on the excised uterus and fallopian tubes which were kept alive by being immersed in oxy-

<sup>1</sup> Abridgment of thesis submitted by Dr. Wilson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.

generated Locke's solution. Rubin (11 and 14) has shown that these fluctuations of pressure are due to tubal peristalsis. The fluctuations are totally absent when the tubes are occluded; they are absent in the dead specimen, and they are not artefacts as they cannot be reproduced by insufflating rubber tubing or the like. The nonpregnant uterus is not responsible for this occurrence, as shown by repeated tests on nonpatent tubes and by actual balloon inflation of the uterine cavity.

Interest was stimulated to correlate the characteristic variables of the pressure curve by fifty instances of high initial pressure which were noted while reviewing the 1,029 kymographic recordings of tubal reaction to transuterine tubal insufflation; in addition, it seemed necessary to determine behavior of the pressure curves in normal and abnormal menstrual cycles for comparison and study.

It has been observed in animals by Rubin, Whitelaw, Corner, Mayer, Newman and Ginzler that there is a change in the contractility of the fallopian tubes at various phases of the menstrual cycle. It has been suggested by Rubin that the hormonal activity of the ovary has an effect on tubal contractions. Since many of the patients in the 343 cases reviewed had a deficient endometrium and an abnormal menstrual cycle, it is of interest to compare the kymographic recordings of transuterine tubal insufflation in these cases with those made in cases in which the menses were normal and other evidences of normal function of the genital tract were present.

The 343 cases were divided into four groups to facilitate study and comparison. Group 1 consists of 154 cases in which insufflation was performed in the last half of the menstrual cycle. Group 2 consists of eighty cases in which tubal insufflation was performed on or before the fifteenth day of the menstrual cycle. The menstrual histories of the patients in these two groups were normal. Group 3 consists of fifty cases in which an initial pressure of 140 mm. of mercury or more was followed by an essentially normal recording of tubal motility. The kymographic recordings of the tubal reaction to insufflation were normal in all the cases except those in group 3. Group 4 consists of fifty-nine cases in which there was gross evidence of a menstrual disturbance. In this group, the disturbances ranged from irregularity of the menstrual cycle to amenorrhea.

#### METHOD OF STUDY

Several variable factors which might affect the characteristics of the pressure curves were considered. It has long been a clinical observation at the Mayo Clinic that the time in the menstrual cycle at which transuterine tubal insufflation is done affects the character of the pressure curve. The eighty patients in group 2, who underwent insufflation early in the menstrual cycle, were compared with the 154 patients in group 1, who underwent insufflation in the last half of the cycle. The histories and the kymograms of the fifty patients in group 3, in which the initial pressure was high, were studied in an attempt to determine whether or not there was any common factor or group of factors that might account for the tubal spasm which resulted in the high initial pressure. The fifty-nine patients in group 4 had irregular or abnormal menses. These patients were studied to determine whether or not the tubal motility was affected by the hormonal imbalance which appeared to be responsible for the abnormal menses. The basal metabolic rate was determined in all cases, as a part of the study of infertility, and was reviewed to determine

whether or not any variation of the tubal contractions might be associated with various levels of the basal rate. It was of interest to compare the pressure curves of patients who received a sedative prior to insufflation with the curves of those who did not receive a sedative. The presence or absence of dysmenorrhea was noted to determine whether or not the tubal contractions of a patient who has dysmenorrhea vary from those of a patient who has painless menses. Finally, it was felt that a consideration of these variable factors, which might affect the type of pressure curve obtained, might indicate whether there is an optimal time in the menstrual cycle at which transuterine tubal insufflation should be performed in order to obtain the most information.

The apparatus used to accomplish transuterine tubal insufflation consists of a tank of carbon dioxide with a reduction valve which is connected to siphometer. One discharge from the siphometer represents 40 c.c. of gas. Two rubber tubes lead from the siphometer; one is connected with a metal cannula which is inserted into the uterine cervix; the other rubber tube leads to a mercury manometer with a float. The float is attached to an ink writer of a kymograph, such as that ordinarily used in physiologic laboratories.

The rate of flow of the carbon dioxide gas was 40 cc. per minute, and remained constant throughout the tests. The drum of the kymograph was turned at a constant speed by a motor.

Under sterile technic, the anterior lip of the cervix was grasped with a tenaculum. A cannula with a rubber guard was placed in the cervix and the insufflation of the uterus and tubes was performed.

Immediately on completion of the uterotubal insufflation, specimens of the endometrium were obtained for microscopic examination. These were obtained with a cannula curet. Two or three strips of endometrium were obtained. The specimens of endometrium were preserved in formalin until they could be sectioned, stained and mounted for microscopic examination.

## RESULTS

Among the 343 patients selected for detailed study, there were 234 who had normal menstrual periods and normal insufflation records. Eighty of these patients (group 2) underwent insufflation on or before the fifteenth day of the menstrual cycle; the remaining 154 (group 1) underwent insufflation in the last half of the cycle.

The patients who underwent transuterine insufflation in the first half of the menstrual cycle required a higher pressure of carbon dioxide gas than did those who underwent insufflation in the last half of the cycle (table I). The amplitude was less and the frequency of the tubal contractions was greater in the cases in which insufflation was performed in the first half of the menstrual cycle.

The other variable factors will be mentioned separately in the consideration of the results in each of these two groups (groups 1 and 2) since there is a definite variation between the curves recorded in the first half of the menstrual cycle and those recorded in the last half of the cycle.

**GROUP 1.** The menstrual cycle and the menstrual flow were normal in the 154 cases in this group. The insufflation was performed on or after the sixteenth day of the menstrual cycle; on the average, it was performed on the twenty-second day of the cycle.

**Basal metabolic rate.** Seventeen patients in this group had a basal metabolic rate of minus 11 or less; seven patients had a basal rate of plus 11 or higher. The kymographic recordings of the tubal reactions of these patients were compared with those of the 130 patients who had a basal metabolic rate ranging between plus 10 and minus 10. No consistent significant difference was demonstrable. This also was true in the other groups of cases.

**Dysmenorrhea.** Dysmenorrhea was present in thirty-five of the 154 cases in this group. In twenty-seven of the thirty-five cases, the dysmenorrhea was of mild or moderate severity



(grade 1 or 2<sup>3</sup>); in the remaining eight cases, the dysmenorrhea was more severe (grade 3 or 4<sup>2</sup>). Statistically there was no significant, consistent difference between the tubal reactions, as recorded by the kymograph, of patients who had dysmenorrhea and patients who did not have dysmenorrhea.

*Sedation.* In thirty-eight of the 154 cases in this group, no sedative was administered before transuterine tubal insufflation was performed. In the remaining 116 cases, 0.10 gm. of pentobarbital sodium was administered orally half an hour before insufflation was performed. Administration of a sedative, even in such small doses as were used in these cases, affects the tubal reaction. The tubal contractions of patients who did not receive any sedative were greater in amplitude and less frequent than those of patients who received a sedative (table II). The pressure required to produce insufflation was lower in cases in

TABLE I

*Differences between kymographic recordings of tubal reaction to increased intra-uterine pressure of carbon dioxide in the first and last half of the menstrual cycle*

MENSTRUAL CYCLE	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY						CONTRACTIONS			
		Initial*		Maximal		Minimal		Amplitude, mm.		Number per cm.	
		Mean	Per-centage error	Mean	Per-centage error	Mean	Per-centage error	Mean	Per-centage error	Mean	Per-centage error
First half	80 (group 2)	92.9	2.72	100	2.54	61.9	2.09	10.3	0.55	0.90	0.096
Last half	154 (group 1)	81.8	2.01	90.4	1.83	46.6	1.38	15.6	0.57	0.68	0.018

\* Pressure required to cause the carbon dioxide to begin to pass through the tubes.

TABLE II

*Effect of sedation on the kymographic recordings of the tubal reaction to transuterine insufflation in cases in group 1*

SEDATIVE ADMINISTERED	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
None	38	77	85	44	18	0.66
Pentobarbital sodium (0.10 gm.)	116	83	92	47	15	0.68

which sedation was not employed. These differences are similar to those seen in the other three groups of cases.

*Anovulatory cycles.* Twenty patients presumably had an anovulatory menstrual cycle at the time of transuterine tubal insufflation. This was determined by the lack of differentiation in the endometrium obtained for microscopic study. The kymographic recordings of the tubal reaction to insufflation in an anovulatory cycle (table III) resemble those of the reaction to insufflation in the early stage of a menstrual cycle. The pressure curves

<sup>2</sup> At the Mayo Clinic we commonly classify the severity of a condition as grade 1, 2, 3 and 4. Thus, grade 1 represents a minimal and grade 4 a maximal degree of dysmenorrhea.

are higher than they are in ovulatory cycles and the tubal contractions are smaller in amplitude and more frequent. These characteristics were present in all pressure curves obtained in patients who gave evidence of the presence of an anovulatory cycle.

GROUP 2. This group includes eighty cases in which insufflation was performed on or before the fifteenth day of the menstrual cycle. All of these patients had a normal menstrual cycle and a normal menstrual flow.

*Basal metabolic rate.* Twelve of the eighty patients had a basal metabolic rate of minus 11 or less. Four patients had a basal metabolic rate of plus 11 or higher. The tubal reactions of the patients who had an elevated or depressed basal metabolic rate did not differ significantly from the tubal reactions of patients who had a basal metabolic rate within normal (plus 10 to minus 10) limits. There was more variation in group 2 than in any other group. In view of the small number of patients and the lack of consistency in all groups, this variation is probably not significant.

*Dysmenorrhea.* Nineteen of the eighty patients in this group complained of dysmenorrhea. In three cases the dysmenorrhea was grade 3 or 4 and in sixteen cases it was grade

TABLE III

*Effect of an anovulatory menstrual cycle on the kymographic recordings of the tubal reaction to insufflation in cases in group 1*

TIME OF INSUFFLATION	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
At anovulatory menstrual cycle.....	20	90.5	102.5	58	11.4	0.82
At ovulatory menstrual cycle.....	134	80.5	88.5	45	16.2	0.65

TABLE IV

*Effect of sedation on the kymographic recordings of the tubal reaction to transuterine insufflation in cases in group 2*

SEDATIVE ADMINISTERED	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
None.....	16	92	95	63	10	0.94
Pentobarbital sodium (0.10 gm.)....	64	93	101	62	10	0.89

1 or 2. The tubal reactions of patients with dysmenorrhea did not vary significantly from those of patients who experienced painless menstrual periods. There was a noticeable variation in the tubal reactions of patients with severe dysmenorrhea (grade 3 or 4), but since this difference was not noted in all the groups and since only three of the patients in this group had severe dysmenorrhea, the difference can not be considered statistically significant.

*Sedation.* Sixteen of the eighty patients did not receive any sedative prior to the transuterine tubal insufflation. In the remaining sixty four cases, 0.10 gm. of pentobarbital sodium was administered orally, thirty minutes before insufflation. In these cases the pressure required to accomplish insufflation of the tubes was higher than it was in the sixteen cases in which sedation was not employed (table IV). In all the other groups, the tubal contractions of patients who did not receive a sedative were larger in amplitude and less frequent than they were in cases in which sedation was employed. These changes were

not as noticeable in group 2 as they were in the other groups. In view of the fact that these changes were very noticeable in the other groups, the lack of conformity in group 2 does not invalidate the changes seen in the other groups, particularly since the tendency toward the same changes is evident in group 2.

**GROUP 3.** This group includes fifty cases in which the initial pressure of the carbon dioxide was 140 mm. of mercury. In each case the pressure dropped following the high initial pressure and the fluctuations in pressure resemble those of normal tracings.

This group of fifty cases was studied in an attempt to determine whether or not there was any associated factor or group of factors which might explain the occurrence of such a behavior of the tubal musculature.

Rubin<sup>12</sup> expressed the opinion that a high initial pressure followed by an essentially normal record of tubal motion is indicative of tubal spasm. In our experience, certain factors such as menstrual dysfunction, dysmenorrhea, an anovulatory menstrual cycle, and insufflation in an early stage of the menstrual cycle, have seemed to be associated with the occurrence of tubal spasm. It seems evident, therefore, that the incidence of menstrual abnormalities is higher in cases in which the kymograms disclose evidence of tubal spasm than it is in an average group of cases of infertility.

**Basal metabolic rate.** The level of the basal metabolic rate did not materially affect the type of tubal contraction in this group.

TABLE V

*Effect of menstrual disturbances on the kymographic recordings of the tubal reaction to insufflation in group 2*

MENSTRUAL STATUS	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
Menorrhagia.....	1	150	150	120	10	0.89
Oligomenorrhea.....	8	156	157	79	21	0.89
Irregular cycle.....	10	170	174	81	16	0.58
Normal cycle.....	31	161	163	82	12	0.70

**Dysmenorrhea.** Dysmenorrhea was much more prevalent in group 3 than it was in any other group. It occurred in seventeen, or 34 per cent. of the cases. There was no significant consistent difference between the tubal contractions of patients with dysmenorrhea and the tubal contractions of the patients who did not have dysmenorrhea.

**Disturbances of menstrual function.** Rubin<sup>14</sup> has reported that the pressure of carbon dioxide required to insufflate the tubes is lower in cases of oligomenorrhea than it is in similar cases in which this menstrual disturbance is not present. He also noted that the tubal contractions were less frequent in cases of oligomenorrhea. These findings were corroborated in group 3 (table V). Since there was only one case of menorrhagia in this group, the effect of this disturbance will not be considered. The tubal contraction of patients who had irregular menstrual cycles differed somewhat from those of patients who had regular cycles and normal menses, but the variation was wide and not constant; therefore, it cannot be considered significant.

**Anovulatory cycles.** In six cases, insufflation was performed in an anovulatory cycle. These six anovulatory cycles were seen in thirty-three cases since insufflation was performed on or before the fifteenth day of the menstrual cycle in seventeen of the fifty cases and a specimen of endometrium was not obtained for biopsy in these cases. In cases in which insufflation is performed at any time in the course of an anovulatory cycle, even if it is performed in the last half of the menstrual cycle, the pressure curve and the tubal contractions

resemble those usually seen in cases in which insufflation is done in the first half of the menstrual cycle. In group 3, this difference was not as marked as it was in the other groups but the tendency was the same (table VI). The pressure curves in an anovulatory cycle are higher, the amplitude of the tubal contraction is smaller and the frequency of the contractions is greater. These effects were more pronounced in groups 1 and 2, but they also are evident in group 3.

*Sedation.* In five of the fifty cases in this group, 0.10 gm. of pentobarbital sodium was administered orally before the insufflation was done. In this group, as in all the others, almost all of the patients who received a sedative had higher pressure curves and smaller and more frequent tubal contractions than did the patients who did not receive a sedative (table VII).

GROUP 4. This group consists of fifty-nine cases in which the menstrual cycles were irregular. Included in this group are those cases in which there was a variation of ten or

TABLE VI

*Effect of an anovulatory menstrual cycle on the kymographic recordings of the tubal reaction to insufflation in group 3*

TIME OF INSUFFLATION	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
At anovulatory menstrual cycle.....	6	159	166	93	13.5	0.61
At ovulatory menstrual cycle.....	27	161	161	74	13.7	0.62

TABLE VII

*Effect of sedation on the kymographic recordings of the tubal reaction to transuterine insufflation in cases in group 3*

SEDATIVE ADMINISTERED	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
None.....	5	151	159	78	19	0.51
Pentobarbital sodium (0.10 gm.)....	45	163	164	83	14	0.66

more days from a twenty-eight cycle. The menstrual cycles were consistently irregular in all cases. Four patients (7 per cent) had menorrhagia, thirteen patients (22 per cent) had oligomenorrhea, seventeen patients (29 per cent) had intermittent or persistent amenorrhea, and twenty-five patients (42 per cent) had an essentially normal menstrual flow when menstruation did occur.

These fifty-nine patients were studied to determine whether or not menstrual irregularities had any significant effect on the kymographic recordings. In eleven of the fifty-nine cases, the transuterine tubal insufflation was done in the early part of the menstrual cycle; in forty-eight cases, it was done in the last half of the cycle. These cases are considered separately (table VIII).

Table VIII shows that there was a difference in kymographic recordings made in the first and second halves of the menstrual cycle. This difference was less marked in cases of menstrual irregularity than it was in cases in which the menstrual cycle occurred regularly. In the cases in which insufflation was performed in the first half of the menstrual cycle, the

frequency and amplitude of the contractions of the tubes were not as great in cases in which the menstrual cycle was regular as they were in cases in which the menstrual cycle was irregular. This may be due to the lack of muscular tone in the cases in which the menstrual cycle was irregular. This also would explain the lower pressure curves in the latter group. The tubal contractions of patients who underwent insufflation in the last half of the menstrual cycle and who had irregular menstrual cycles are smaller and more frequent than those of patients who underwent insufflation in the last half of the menstrual cycle and had regular menstrual cycles. This finding again could be explained by decreased muscular tone of the fallopian tubes of the patients who had an irregular menstrual cycle.

*Basal metabolic rate.* The basal metabolic rate apparently makes little difference in the character of the kymographic tracings obtained by transuterine tubal insufflation. A slight difference was present but this was too small to be significant statistically. In none

TABLE VIII

*Effect of irregular menstrual cycle and stage of the menstrual cycle on the kymographic recordings of the tubal reaction to transuterine insufflation*

TIME OF INSUFFLATION	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
First half of irregular cycle.....	11	82.7	98.2	60.9	11.4	0.82
First half of regular cycle.....	80	92.9	100	61.9	10.3	0.90
Last half of irregular cycle.....	48	77.7	86.5	49.4	12.4	0.74
Last half of regular cycle.....	154	81.8	90.4	46.6	15.6	0.68

TABLE IX

*Effect of menstrual disturbances on the kymographic recordings of the tubal reaction to insufflation in group 4*

MENSTRUAL STATUS	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
Menorrhagia.....	4	94	94	54	10	0.78
Oligomenorrhea.....	13	78	94	49	11	0.74
Amenorrhea.....	17	71	78	48	11	0.76
Normal.....	25	82	93	55	14	0.74

of the other groups did the level of the basal metabolic rate materially affect the character of the tubal contractions as recorded by the kymograph.

*Dysmenorrhea.* Thirteen of the fifty-nine patients in this group complained of dysmenorrhea. In only one case was the dysmenorrhea severe enough to be classified as grade 3. In the other twelve cases it was classified as grade 1 or grade 2. There was no consistent significant difference between the tubal reaction of patients who had dysmenorrhea and those who did not. This finding was consistent in all the four groups of cases.

*Evidence of menstrual abnormality.* In four cases in this group, the patients had menorrhagia and irregular menstrual cycles. The kymographic recording of tubal motion in these cases did not differ significantly from those of patients who had normal menses but irregular menstrual cycles (table IX).

Oligomenorrhea was present in thirteen (22 per cent) of the fifty-nine cases. The dif-



ference in the tubal contractions of patients who had oligomenorrhea and irregular menstrual cycles and the tubal contractions of patients who had a normal menstrual flow and irregular cycles is great enough to be noted. There was an evident tendency toward lower pressure curves in the cases of oligomenorrhea.

Seventeen (29 per cent) of the patients in this group had amenorrhea. The duration of the amenorrhea ranged from four months to six years. As Rubin has noted, the tubal contractions of patients who have amenorrhea differ from the tubal contraction of patients who have normal menses. In the cases of amenorrhea, the pressure curves were lower than those in cases in which no menstrual abnormality was present. The amplitude of the contractions was smaller in cases of amenorrhea.

*Sedation.* Eight of the fifty-nine patients did not receive any sedative before tubal insufflation was performed. In cases in which sedation was not employed the pressure of the gas required to insufflate the tubes was decreased, the amplitude of the contraction waves was increased, and the frequency of the waves was decreased, in comparison with the

TABLE X

*Effect of sedation on the kymographic recordings of the tubal reaction to transuterine insufflation in cases in group 4*

SEDATIVE ADMINISTERED	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
None.....	8	65	74	49	14	0.71
Pentobarbital sodium (0.10 gm.)....	51	81	91	52	12	0.77

TABLE XI

*Effect of stage of menstrual cycle on the kymographic recordings of the tubal reaction to insufflation in cases in group 4*

STAGE OF MENSTRUAL CYCLE	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
First half.....	11	82.7	98.2	60.9	11.4	0.82
Last half.....	48	77.7	86.5	49.4	12.4	0.74

contraction waves of patients who received a sedative (table X). These differences were essentially present in all of the four groups, with the exception of the frequency, which varied in group 2.

*Insufflation in the first half of the menstrual cycle.* In eleven of the fifty-nine cases, insufflation was performed on or before the fifteenth day of the menstrual cycle. The tubal reactions were distinctly different in the first and second halves of the menstrual cycle (table XI). The pressure required to insufflate the tubes was greater in the first half of the cycle. The amplitude of the contractions was decreased and the frequency of the contractions increased when the insufflation was performed in the first half of the menstrual cycle.

*Anovulatory menstrual cycles.* Twenty-two of the fifty-nine patients had an anovulatory cycle at the time of transuterine tubal insufflation. This was deduced by the lack of differentiation of the endometrium obtained for microscopic study at the time of insufflation. In the other groups the kymographic recording obtained during an anovulatory cycle re-

sembled a recording obtained in the first half of the menstrual cycle in that the pressure curves were higher, the amplitude of the contractions was lower, and the frequency of the contractions was greater. Such findings were not consistent in the twenty-two cases in group 4 in which anovulatory cycles were present. In the cases in group 4, the pressure required to produce insufflation was lower in the anovulatory cycle than it was in the ovulatory cycle (table XII). This may be explained by the fact that fifteen of the twenty-two patients who had anovulatory cycles also had amenorrhea. The tubal reaction of patients who had amenorrhea has been described previously and the amenorrhea may explain the low pressure curves in eleven of the cases of anovulatory cycle. The pressure curves were lower and the frequency of the contraction was greater in the twenty-two cases in which an anovulatory cycle was present.

TABLE XII

*Effect of an anovulatory menstrual cycle on the kymographic recordings of the tubal reaction to insufflation in cases in group 4*

TIME OF INSUFFLATION	CASES	PRESSURE OF CARBON DIOXIDE, MM. OF MERCURY			CONTRACTIONS	
		Initial	Maximal	Minimal	Amplitude, mm.	Number per cm.
At anovulatory menstrual cycle.....	22	78.9	84.5	49.1	10.3	0.80
At ovulatory menstrual cycle.....	26	78.5	91.1	50.3	13.4	0.72

## COMMENT

*Inflation in the first and last halves of the menstrual cycle.* There is a considerable difference between the tubal reaction to increased intra-uterine pressure of carbon dioxide gas as measured by the kymograph in the first and last halves of the menstrual cycle. Rubin (10 and 12) has shown that higher pressures are necessary to insufflate the tubes from the tenth to the sixteenth day, but he said that if the inflation is done earlier than the tenth day or later than the sixteenth day the pressure required is less. This was not confirmed in the study of these 343 cases. The eleventh day of the cycle was the average date of the insufflation in cases in which insufflation was performed in the first half of the cycle. In cases in which insufflation was performed in the last half of the menstrual cycle, the average day of insufflation was the twenty-second day of the menstrual cycle. The pressures required to produce insufflation in the first half of the menstrual cycle were higher than were the pressures required in cases in which insufflation was done in the last half of the menstrual cycle. The amplitude of the tubal contractions was less and the contractions were more frequent in cases in which the insufflation was performed in the first half of the menstrual cycle.

The higher pressures and the smaller and more frequent contractions that are characteristic of a kymographic recording of the tubal reaction to insufflation in the first half of the menstrual cycle may be a reflection of increased muscular tone of the fallopian tubes during this period. The increased muscular tone is perhaps a result of the predominant estrogenic influence during the first half of the menstrual cycle. It has been proved by Geist and others that the adminis-

tration of estrogens to women who are past the menopausal age will cause (1) an increase of the pressure required to insufflate the fallopian tubes, and (2) an increase in size and frequency of the tubal contractions.

Patients who undergo transuterine tubal insufflation in the first half of the menstrual cycle complain much more of discomfort than do those who undergo insufflation in the last half of the cycle. This could be explained by the increased irritability of the musculature of the fallopian tubes during the first half of the menstrual cycle and also by the increased pressure necessary to insufflate the fallopian tubes in the first half of the menstrual cycle.

Rubin (13) has stated that the interval of choice for uterotubal insufflation is from the fourth to the seventh day after the cessation of the menstrual flow, because the endometrium then is in a relatively quiet stage and there is no danger of interfering with an existing pregnancy. He also stated that during these days the possibility of endometrial dislocation and air embolism is lessened. It has long been the procedure at the clinic to do transuterine tubal insufflation in the last half of the menstrual cycle, preferably about the twenty-first to twenty-third day. This time is chosen because a specimen of endometrium usually is obtained for biopsy immediately after the insufflation. Microscopic examination of a specimen of endometrium obtained at this time of the cycle is valuable in determining the development of the endometrium. A transuterine tubal insufflation done in the last half of the cycle requires less pressure and is noticeably less painful to the patient. No ill effects have been caused as far as infection or air embolism are concerned by doing the insufflation in the last half of the cycle.

*High initial pressure.* In fifty cases the kymographic recordings showed an initial pressure of 140 mm. of mercury or more; the range was from 140 to 200 mm. of mercury. After this high initial pressure, the pressure dropped gradually and the manometric oscillations were typical of those associated with normal tubes. Rubin (12) has noted this type of pressure curve and has attributed it to spasm. He said that it is the result of a spasm of the tubo-uterine junction.

The histories of patients who required a high initial pressure for insufflation were carefully studied to determine whether or not there might be some association between dysmenorrhea, menstrual dysfunction and anovulatory cycles, and this reaction of the tubes.

In forty of the fifty cases there was some form of menstrual abnormality, such as dysmenorrhea, oligomenorrhea, menorrhagia, or an anovulatory cycle (as determined by the lack of differentiation of the endometrium). The incidence of tubal spasm was higher in cases in which insufflation was done in the first half of the menstrual cycle. This may be due to the higher pressure necessary to accomplish the insufflation, or it perhaps may be due to the increased irritability of the musculature of the tubes. The high percentage of patients who had dysmenorrhea, menstrual abnormalities, and anovulatory cycles may be significant.

The oral administration of 0.10 gm. of pentobarbital sodium before the insufflation did cause an appreciable lessening of the spasm.

*Evidence of disturbed menstrual function.* In reviewing the menstrual histories of the 343 infertile patients who underwent transuterine tubal insufflation, it was noted that there were fifty-nine patients who had evidence of variations from the normal menstrual cycle and flow. Twenty-five patients had a normal flow but an irregular cycle. A menstrual cycle was adjudged irregular if the onset of menstruation varied more than ten days from an interval of twenty-eight days. Thirteen patients had oligomenorrhea. A diagnosis of oligomenorrhea was made if the patient menstruated for three days or less and if she used no more than two pads on any one day. Seventeen patients had amenorrhea. If a patient had not menstruated in four or more months she was considered to have amenorrhea. Four patients had menorrhagia. These patients had profuse menses which lasted from five to ten days.

Rubin (13) suggested the possibility of estimating ovarian function clinically by the character of the rhythmic tubal contractions as recorded by the kymograph during tubal insufflation. Many other investigators have indicated a relationship between cyclic changes in the motility of the fallopian tubes and cyclic changes in the ovaries. Corner, in 1923, observed a variation of the tubal contractions with the various stages of the menstrual cycle. Experimental studies by Reynolds, Wislocki and Guttmacher, Andersen, Lee and others have demonstrated similar cyclic changes.

Oligomenorrhea was present in twenty-one of the 343 cases. The pressure required to insufflate the tubes in these cases was less than it was in the cases in which oligomenorrhea was not present. There was a tendency for the frequency of the tubal contractions to be decreased in cases in which oligomenorrhea was present but this was not significant statistically. The change in the amplitude of the contractions also was not significant.

Rubin (13) also has noted that the pressure required to insufflate the tubes is less in cases in which the menstrual flow is scanty than it is in cases in which the flow is normal. This change may be explained by the diminished muscular tone, which is manifested by a decrease in the frequency of the tubal contractions.

Amenorrhea was present in seventeen cases. The pressure required to insufflate the tubes in these cases was distinctly lower than the pressure required in cases in which there was no menstrual abnormality. The amplitude of the tubal contractions was less than it was in cases in which there was no menstrual abnormality. The frequency of the contractions also was decreased in the cases of amenorrhea. Rubin (13) observed the same changes in cases of amenorrhea and he expressed the opinion that they were attributable to decreased muscular tone, which may be due to the deficient ovarian function that also is responsible for the amenorrhea.

Geist, Salmon and Mintz, and Davids and Bender reported their findings in cases in which tubal insufflation was performed on women who were past the menopausal age. The pressure required to insufflate the tubes in these cases was less than it was in cases in which the patients had not reached the menopausal age. The amplitude and frequency of the tubal contractions also were less in the cases in which the patients were beyond the menopausal age. Geist, Salmon

and Mintz said that the administration of estrogenic hormone to women who are past the menopausal age will increase the pressure required to produce subsequent insufflation and also will increase the amplitude and frequency of the tubal contractions.

In forty-eight of the 343 cases, the menstrual cycle was irregular. In these forty-eight cases, the pressure required to produce inflation of the tubes was less than it was in cases in which the menstrual cycle was regular. The amplitude and frequency of the tubal contractions also were less than they were in cases in which the menstrual cycle was regular. This difference in the amplitude and frequency of the tubal contractions may be due to a diminution of the muscular tone of the fallopian tubes in cases in which the menstrual cycle is irregular.

*Anovulatory cycle.* In forty-eight of the 343 cases, an anovulatory menstrual cycle was present at the time insufflation was performed. This was deduced by the absence of differentiation of the endometrium obtained for biopsy immediately after insufflation was performed. The pressure required to produce insufflation in these cases was similar to that required to produce insufflation during an early stage of the menstrual cycle. In the forty-eight cases in which an anovulatory menstrual cycle was present, the pressure required to produce insufflation was higher than it was in cases in which an ovulatory cycle was present. The amplitude of the tubal contractions was less in cases in which an anovulatory cycle was present and the contractions were more frequent. This pressure curve was not present in fifteen of the twenty-two cases of anovulatory menstrual cycles occurring in association with amenorrhea that were included in group 4. Their pressure curves demonstrated a lower inflation pressure and less frequent contractions.

The increase in the pressure required to produce insufflation pressure and the smaller and more frequent tubal contractions in cases of an anovulatory cycle, except in group 4, may be due to the increased muscular tone of the fallopian tube owing to the continuing estrogenic influence from the lack of ovulation.

*Dysmenorrhea.* In all of the cases in which dysmenorrhea was present it was of the spastic type. The pain in all cases was cramplike in nature and usually began from one day to a few hours before the onset of the menstrual flow and persisted for two or three days.

On clinical, rather than on scientifically demonstrable, grounds, the frequently crampy character of spastic dysmenorrhea has been rather generally, although not unanimously, accepted as being due to exaggerated uterine contractility (Novak). It has been postulated that patients who have spastic dysmenorrhea perhaps have an increased activity of the musculature of the fallopian tubes and that this increased activity may be recorded by the kymograph during transuterine tubal insufflation. With this view in mind, the kymographic recordings made in cases of spastic dysmenorrhea were compared with those made in cases in which spastic dysmenorrhea was not present. There was no significant difference in the tubal reactions to insufflation in the two groups of cases.

Dysmenorrhea is a subjective symptom which is extremely difficult to evaluate,



since individual responses to pain stimuli vary greatly. The variation in the amplitude and frequency of the tubal contractions was greater in the cases in which dysmenorrhea was present than it was in the cases in which dysmenorrhea was not present but the variations were not consistent enough to be significant. Perhaps the difficulty in evaluating dysmenorrhea might be responsible for the lack of uniformity of the findings.

*Sedation.* In 80 per cent of the cases, 0.10 gm. of pentobarbital sodium was administered orally before insufflation was performed. This was done to lessen the anxiety and tension, which commonly are present, and also to provide analgesia. Pentobarbital sodium was used because of its prompt and comparatively brief action. The brief action was particularly desirable since the transuterine tubal insufflation was done in the office in the cases in this series.

Rubin (13) has shown that tubal contractions are less frequent when the patient is anesthetized to the extent that consciousness is lost. It was found that the oral administration of as little as 0.10 gm. of pentobarbital sodium affected the type of tubal reaction noticeably. In all of the four groups, the findings were essentially the same. In those cases in which sedation was employed the amount of pressure required to insufflate the tubes was consistently higher than it was in the cases in which sedation was not employed. In cases in which sedation was employed, the tubal contractions were smaller in amplitude and more frequent than they were in cases in which sedation was not employed.

The higher pressure curves in cases in which sedation was employed may be due to the lessened motility of the smooth muscle of the fallopian tubes, thus causing less frequent muscular contractions resulting in a higher pressure necessary to accomplish insufflation. This explanation was suggested by Sollmann, who stated that the motility of the gastro-intestinal tract is significantly reduced and that the emptying time of the stomach is delayed by pentobarbital. He also stated that ureteral contractions are depressed by moderately large doses of pentobarbital, but that adequate stimulation by distention of the ureter or administration of pilocarpine produces peristalsis. The oral administration of 0.10 gm. of pentobarbital sodium apparently does affect the conduction of stimuli by the nerve pathways to an extent that can be recorded.

Patients who receive a sedative prior to transuterine insufflation tolerate the procedure better and complain less of discomfort than do those who do not receive a sedative.

*Basal metabolic rate.* The basal metabolic rate was determined in all of the 343 cases. The kymographic recordings of tubal reaction to transuterine tubal insufflation were studied in an attempt to determine whether or not the level of the basal metabolic rate had any effect on the tubal reaction. In 276 cases, the basal metabolic rate was between plus and minus 10; in sixteen cases it was plus 11 or higher, and in fifty-one cases, it was minus 11 or less.

There was no appreciable difference between the kymographic recordings of tubal reaction to transuterine tubal insufflation in any of the groups of cases.

## SUMMARY AND CONCLUSIONS

*Insufflations in the first and last halves of the menstrual cycle.* The reaction of the musculature of the fallopian tubes to transuterine tubal insufflation with carbon dioxide varies according to the period in the menstrual cycle at which the insufflation is performed. Kymographic recordings revealed that the pressure required to insufflate the tubes in the first half of the menstrual cycle was higher than that required to accomplish insufflation in the latter half of the cycle. The tubal contractions are smaller in amplitude and more frequent in the first half of the menstrual cycle.

*Tubal spasm.* No satisfactory explanation was reached as to the cause of tubal spasm. In a large proportion of the cases in which there was evidence of tubal spasm, menstrual disturbances were present or the insufflation was performed at the time of an anovulatory menstrual cycle or in the first half of a menstrual cycle.

*Disturbances of menstrual function.* In cases in which oligomenorrhea was present, the tubal reaction to insufflation differed from that observed in cases in which there was no menstrual disturbance. In the cases of oligomenorrhea, the pressure required to produce insufflation was less than it was in cases in which the menstrual flow was normal. The amplitude and frequency of the tubal contractions also were somewhat less in the cases in which oligomenorrhea was present.

In cases of menorrhagia, the tubal reaction to insufflation did not differ appreciably from that observed in cases in which the menses were normal. The number of cases of menorrhagia was too small to warrant definite conclusions regarding the effect of menorrhagia.

Patients who had amenorrhea had a different tubal reaction to insufflation than did patients who had normal menses. The pressure required to produce insufflation was less than it was in cases in which the menses were normal. The amplitude and frequency of the tubal contractions also were less in cases of amenorrhea.

In cases in which the menstrual cycles were irregular, the pressure required to produce insufflation had a tendency to be lower than the pressure required in cases in which the menstrual cycles were regular. The amplitude and frequency of the tubal contractions also tended to be less in cases in which the menstrual cycles were irregular.

*Anovulatory menstrual cycles.* The tubal reaction to insufflation at the time of an anovulatory menstrual cycle resembled the tubal reaction seen when the insufflation was done in the first half of the menstrual cycle. In the cases in which the insufflation was performed at the time of an anovulatory menstrual cycle, the pressure required to produce insufflation was less than it was in cases in which insufflation was performed at the time of an ovulatory menstrual cycle. The amplitude and frequency of the tubal contractions also were less in cases in which insufflation was performed at the time of an anovulatory menstrual cycle.

*Dysmenorrhea.* The presence of dysmenorrhea did not have any appreciable effect on the tubal reaction to insufflation.

*Sedation.* The oral administration of 0.10 gm. of pentobarbital sodium had a definite effect on the tubal reaction. Higher pressures were required to produce insufflation in cases in which a sedative was administered. The amplitude and frequency of the tubal contractions were less in cases in which pentobarbital sodium was administered. Although the effects of sedation varied in some cases, the general effect was the same in all cases.

*Basal metabolic rate.* The basal metabolic rate did not have any effect on the tubal reaction to insufflation.

*Optimal time for the performance of insufflation.* The most opportune time for the performance of diagnostic transuterine tubal insufflation is in the last half of the menstrual cycle, that is from about the twenty-first to the twenty-fourth day. The tubal response at this time is more uniform, the amount of pressure required to produce insufflation is less, and the pain associated with the procedure is less at this time. A specimen of endometrium should be removed for biopsy in cases of infertility.

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## THE RUBIN TEST

### UTERO-TUBAL INSUFFLATION, ITS ORIGIN AND SCOPE

SEYMOUR WIMPFHEIMER, M.D.

(New York, N. Y.)

The Rubin Test, considered as one of the most monumental contributions to gynecology, was the result of the lifelong effort of its discoverer to develop and perfect the technique of utero-tubal insufflation.

Before the advent of utero-tubal insufflation it was impossible to establish one of the main causes of sterility, except by operation. The examination was almost entirely limited to palpation of the female genital tract. Operations for sterility were performed on the cervix and uterus without appreciating that the cause might be in the Fallopian tubes. In cases of sterility diseased Fallopian tubes frequently gave no palpatory evidence of closure. In the absence of signs of pelvic inflammation, pathology of the Fallopian tubes was not considered an etiological factor. Only after the failure of other methods of therapy, was attention directed toward investigating the Fallopian tubes. In these cases an exploratory laparotomy was the only means of determining the status of the tubes. Despite the comparative safety of this procedure, gynecologists were reluctant to perform an operation to ascertain whether the Fallopian tubes were open or closed. The need for a non-surgical test to determine tubal patency was therefore apparent.

Among Dr. Rubin's many interests, the study of the causes of sterility was paramount. He realized that disturbances within the Fallopian tubes were important factors in producing sterility. He therefore began investigating the physiological function of the Fallopian tubes, both *in vivo* and after extirpation. The results of these investigations proved that tubal disease was a frequent cause of sterility.

In 1913 Dr. Rubin (1) made his first attempt to visualize the lumen of the oviducts by injecting them with an x-ray opaque medium (Collargol). Finding Collargol objectionable, Rubin tried several of the halogen salts. These radio-opaque substances were found disadvantageous, because of chemical irritation, intratubal inspissation and limited radio-opacity in the strengths employed. Rubin therefore substituted oxygen, which had been utilized previously in producing pneumoperitoneum. But instead of introducing it by puncture into the peritoneal cavity, Rubin introduced it via the uterus. After years of experimentation he tested his method at Mount Sinai Hospital in 1919. Every means was taken to make this test a safe procedure. Therefore, certain precautions and devices were implemented to control the amount of oxygen insufflated (siphon volume meter) and the pressure under which it was permitted to flow (manometer) (2). The indications and contraindications were carefully considered to minimize any dangers of misapplying the test. It had been noted that the shoulder pain and epigastric distress appreciated by patients subjected to trans-



peritoneal pneumoperitoneum with oxygen had to be reduced substantially in order to make the test tolerable. With this observation in mind, small amounts of oxygen were insufflated through the uterus.

Rubin recognized the possibility of embolism as a result of oxygen or air insufflation via the uterus. He also noted that the epigastric distress and the pains in the shoulder were prolonged when oxygen was used. After considering other gases, he finally adopted carbon dioxide, which was found to be more soluble in the blood and more rapidly absorbed and therefore free from the danger of embolism. Moreover, the intensity and duration of the shoulder pains were lessened.

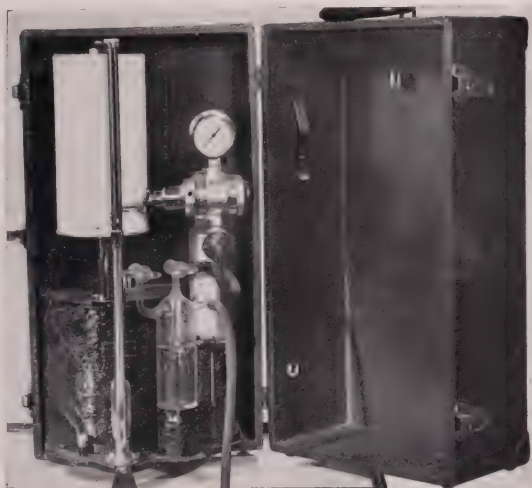


FIG. 1. Utero-tubal insufflation apparatus in portable case (Rubin apparatus).

The rate of insufflation was recognized as an important factor, since he found that a more controlled flow diminished the spasm of the uterine musculature. A comparison of the results achieved by this refinement in technique enabled him to evaluate the results of subsequent tests for diagnostic and therapeutic purposes.

Rubin was still not content with the information obtained by the technique as it had been developed. He, therefore, proceeded to perfect the test in 1925, by the addition of a kymograph. At the same time a safety valve was introduced to prevent attaining excessive pressures beyond 200 mm. Hg (fig. 1). It was now possible to obtain a record of utero-tubal insufflation called the tubograph (3).

A pattern was established for normal physiological function, and another for abnormal deviations produced by alterations in the tubes. With this addition the graphic representation of rhythmic contractions noted with normal tubal

patency could be differentiated from irregular atypical contractions which characterized abnormal tubes. The improved apparatus permitted the pressure, the rate of flow and the volume of gas to be readily determined and kept constant.

Although others have tried to simplify the technique of utero-tubal insufflation, the perfected apparatus devised by Rubin in 1925 is the simplest and permits a graphic recording of normal and abnormal tubal function.

The Rubin Test is most favorably performed from 4-7 days after the cessation of a regular menstrual period (4). The patient is examined before each test in order to exclude the presence of any inflammatory condition which would contraindicate the performance of the test. Through a bivalve speculum the cervix and vagina are cleansed, the cervical mucus aspirated, and an antiseptic is applied to the external os. The uterine cannula adapted for the test is then tested for patency by permitting the carbon dioxide to bubble through into a dish containing a small amount of sterile solution. The gas flow is regulated to a rate flow of one syphon pulsation to 30 seconds. The pressure reduction valve is set at 15 lbs., so that the force to which the carbon dioxide is subject during insufflation, is twice that of the atmospheric pressure. As the capacity of the syphon meter is 30 cc., 60 cc. of carbon dioxide are delivered with each syphon pulsation.

The apparatus is tested for any leaks in the system. The cannula with its acorn tip is then inserted into the uterine cavity; the release valve is closed when the syphon flows to the bottom of the U tube in the glass volume meter. This now enables the carbon dioxide to be insufflated under air tight conditions at the uniform rate flow of 1 cc. to 1 second of time or 60 cc. per minute. The spring motor controls the rotation of the kymograph drum at a definite speed. The graph sheet is divided by lines denoting 1 minute intervals. Horizontal lines are graded for 10 mm. Hg pressure levels. It takes 10 minutes for a complete revolution of the drum. The graph obtained during utero-tubal insufflation may be entered into the record of the patient's history and compared with future records. In the average case one to two pulsations delivering 60 to 120 cc. of carbon dioxide are sufficient for the test. The duration of the test is from 1 to 2 minutes (5).

It is important to note any retrograde regurgitation of carbon dioxide through the cervical canal. At the completion of the test the vagina is again wiped dry and a sterile piece of gauze or tampon may be inserted. The patient is then permitted to assume the sitting position and in less than two minutes she will complain of pain in one or the other shoulder if the tubes are patent. The shoulder pain is the result of a viscerosensory reflex conducted through the 3rd, 4th and 5th cervical nerves, which have a common spinal origin with the phrenic nerve, whereby the pain is referred. A fluoroscopic examination reveals the gas below either leaf of the diaphragm. It is best seen on the right side. If found only on the left side, the gas may be confused with the normal bubble in the stomach. To make certain that a subphrenic pneumoperitoneum is present, one instructs the patient to recline on her left side and make pressure over her right ribs. This forces the gas to the right subphrenic space where it can now be seen with the fluoroscope. The pain is now referred to the right shoulder when the patient assumes the vertical position. Even without a fluoroscope this ma-

noeuver is diagnostic. The pain in the shoulder causes comparatively slight discomfort and persists only for a very brief duration. Placing her in the Trendelenburg position causes the pain to disappear within a few minutes. To lessen any apprehension it is wise to gain the patient's confidence by assuring her of the minimal amount of discomfort resulting from the test.

The tubograph may be divided into several components: (a) the initial rise denoting the entrance of carbon dioxide into the uterine cavity, followed by a drop which occurs when the gas enters the tubes through the utero-tubal ostium and emerges from the fimbriated end of the tube; (b) the level at which the gas flows through the tube signifies the tonicity of the utero-tubal musculature; (c) the oscillations denote the contractions and relaxations of the tubes; (d) the amplitude of the oscillations denote the force of the tubal muscle.

Rubin's studies did not end with mere attempts to perfect the apparatus. He conducted considerable research trying to elucidate the mechanical and physiological phenomena associated with the test. In 1927 he published the results of his investigations proving conclusively that the fluctuations of the mercury column in the manometer and their graphic representation are due to tubal contractions (6). In addition, he showed that the tubal contractions depend upon ovarian function, and therefore vary both in frequency and in amplitude with the various phases of the menstrual cycle. They are also affected by the menopause and by hypo-ovarian function. In these conditions the kymographic curves when present are shallow and less frequent. The present apparatus not only permits the study of the mechanical and hormonal regulation of the tubes, but also affords an opportunity to study the effects of various pharmacological products upon the Fallopian tubes.

Typical tubographs have been described by Rubin for normal and abnormal Fallopian tubes. In normal tubal patency there is an initial rise in pressure to about 100 mm. of mercury followed by a fall in pressure of 1-20 mm. Hg, denoting the passage of carbon dioxide through the utero-tubal and fimbriated ostia. Then the pressure rises and falls in rhythmic fashion, synchronous with the contractions and relaxation of the tubes usually 3-4 per minute (fig. 2). Abdominal muscle straining may cause a slight rise at one point, but does not affect the rhythmic character of the curve, unless this straining is prolonged.

In non-patent tubes the pressure rises to 200 mm. of mercury, which is the maximum pressure recommended for the average patient. Following this trial the pressure is permitted to fall by releasing the valve. The test is repeated and the pressure maintained at 200 mm. Hg by stopping the gas flow, in order to determine whether the closure is due to an organic cause or muscle spasm (fig. 3). Obviously, when the tubes are closed there is no subphrenic pneumoperitoneum and therefore no shoulder pain.

In strictured or partially patent tubes the pressure rises to about 150 mm. of mercury and then falls gradually in a curved or steep fashion without describing any of the curves characteristic of rhythmic contractions (fig. 4). These patients also complain of some shoulder pain, and a subphrenic pneumoperitoneum is as a rule demonstrated.

In utero-tubal spasm the pressure rise may reach from 120 to 200 mm. of mercury when there is a sharp fall to the level of between 30-60 mm. Hg pressure after which contractions will follow similar to those of normal patent tubes (fig. 5). Here also shoulder pain and gas under the diaphragm can be noted. In a few cases where spasm is suspected anti-spasmodics may be used to overcome the muscular spasm. Rubin has found these to be seldom necessary.

Rubin (4) has been able to localize the tubal obstruction by observing the location of the pain and by auscultation of the abdomen. If the obstruction is at the uterine end of the tubes, the patient complains of pain in the suprapubic region. When the obstruction is in the ampulla or fimbriated ends of the tubes the pain is more lateral. At the same time "head zones" may be elicited in the region of the discomfort. Moreover, auscultation may be helpful in localizing the site of the obstruction. In normal tubes, auscultation usually elicits

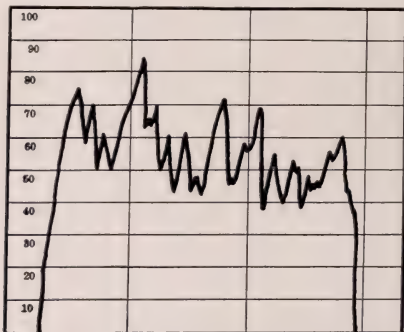


FIG. 2. Normal tubal patency. Initial pressure rise to 75 mm. Hg followed by drop and rhythmic fluctuations for 2½ minutes corresponding to normal tubal contractions.

a purring sound on both sides of the pelvis, synchronous with the rhythmic drop in pressure corresponding to the relaxed phases of the tubal contractions. The silent intervals coincide with the contractions of the tubal musculature and correspond to the recurrent rises in pressure on the graph. In tubal closure these sounds are absent. However, when the souffle is heard on one side and absent on the other it indicates a closed or spastic tube on one side and an open tube on the other side. The character of the souffle varies with the degree of patency. In normal tubes it is intermittent and regular, while in strictured tubes it is more or less constant.

By carefully observing these significant signs and symptoms during tubal insufflation, Rubin has been able to localize the site of tubal obstruction without resorting to the injection of radio-opaque fluids.

Rubin (5) has listed the following aims for the use of utero-tubal insufflation:

1. To determine the status of tubal patency or non-patency.

2. To test patency postoperatively and maintain patency of the newly formed stoma.

3. To verify the success of the operative or non-operative technique for sterilization.

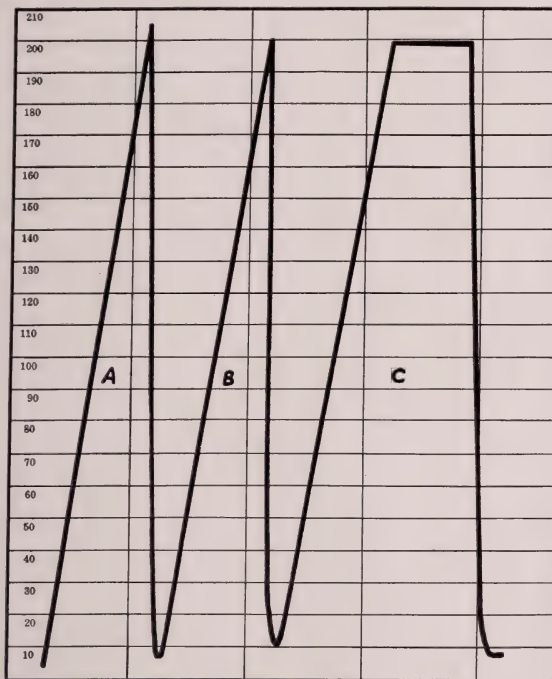


FIG. 3. Tubal non-patency. Pressure rise to 200 mm. Hg. Gas released through safety-valve-drop to zero-gas allowed to flow into uterus; again pressure rise to 200 mm. Hg and released to zero followed by a third insufflation to 200 mm. Hg when gas valve is shut. Pressure is maintained at 200 mm. Hg for about a minute when the cannula is removed.

4. To determine secondary effects upon the tubes, following induced abortions, uterine retro-displacement, appendicitis, tubal pregnancy and myomectomy.

5. To study the physiology of the tubes, as in functional amenorrhea, the menopause and cases castrated by x-ray.

6. To determine the tubal status in cases where contraceptive measures are contemplated.



7. To produce a pneumoperitoneum as an aid in the diagnosis of intra-abdominal lesions.
8. To improve the status of adherent and strictured tubes, as a substitute for laparotomy.
9. To treat certain cases of dysmenorrhea.
10. To assay clinically the biodynamics of hormones and other drugs.

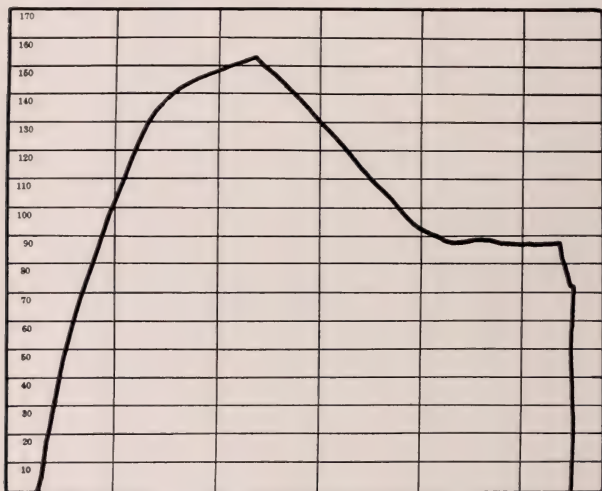


FIG. 4. Tubal strictures. Initial pressure rise to 150 mm. Hg in parabolic fashion followed by gradual drop in pressure over an interval of  $3\frac{1}{2}$  minutes without fluctuations indicating absence of tubal contractions.

He also lists a number of conditions contraindicating utero-tubal insufflation: pregnancy, acute or subacute pelvic inflammation, genital bleeding, pelvic tumors, pelvic tenderness without other evidences of pelvic inflammation, the premenstrual phase and any serious illness.

Though utero-tubal insufflation was primarily developed as a diagnostic procedure, Rubin (7) has demonstrated a therapeutic effect, especially when the kymographic method is employed. In a series of 3,200 cases of sterility in which 590 pregnancies eventually resulted, insufflation was the only treatment in 386 (65.12 per cent). The time elapsing between insufflation and conception could be determined in 573 cases. Rubin noted that 378 or 64.67 per cent of the pregnancies occurred within six months of the test, while 108 occurred within the following six months. One hundred and fifty-eight patients became pregnant within one month after insufflation, while 228 patients or 38.64 per cent became

gravid within two months after insufflation. Many of these patients had been sterile for five years or more.

The therapeutic effect of insufflation is particularly noteworthy in cases of strictured tubes or tubes exhibiting various degrees of impaired patency. In this

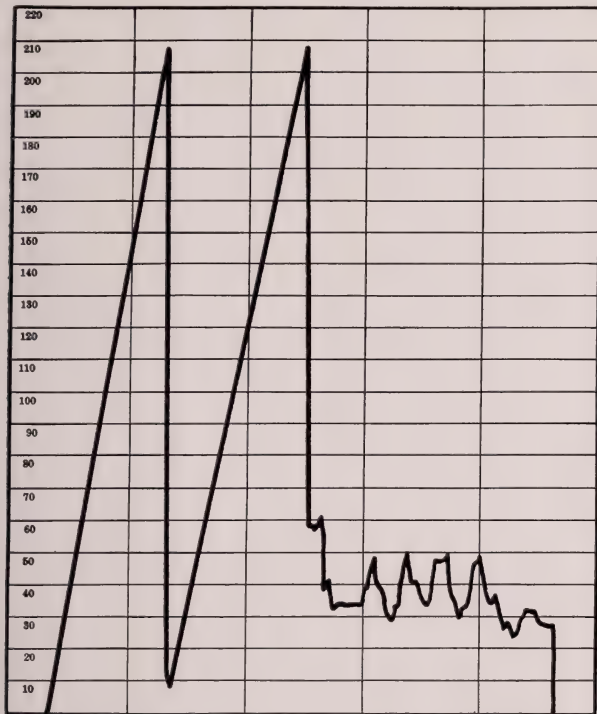


FIG. 5. Tubal spasm (hypertonicity). Initial pressure rise to 200 mm. Hg when gas is released to zero. A second insufflation shows high pressure with sharp spontaneous drop and no cervical regurgitation followed by rhythmic fluctuations as in normal tubal patency.

group, Rubin noted that 46 per cent of the pregnancies resulted when tubal insufflation was the only treatment employed.

The rationale of this effect has been the subject of much discussion. According to Rubin the effect is due either to a dilatation of the cervix, the removal of a cervical mucus plug during the test, or the direct effects on the Fallopian tubes.

Repeated utero-tubal insufflation has been used in conjunction with diathermy and other measures, and has been found to be of distinct therapeutic value eventually in opening tubes which had been previously obstructed. In addition, utero-tubal spasm due to an underlying emotional disturbance, has been found to respond to tubal insufflation.

Utero-tubal insufflation with the present perfected apparatus has distinct advantages over the use of opaque x-ray media, because; (1) x-ray films are unnecessary; (2) it obviates pelvic reactions, caused by the injection of opaque media, which have been found to remain embedded in the pelvis for many years; (3) utero-tubal insufflation may be repeated safely many times.

It is now over 27 years since Rubin first presented the technique of utero-tubal insufflation. The test has been adopted universally. Since its introduction many thousands of tests have been performed. It has served as a stimulus to research in the etiology of sterility. This interest has become so marked that one might call this era in gynecology the insufflation era, in contrast to the pre-insufflation era with its comparatively fruitless period of research.

Though gynecologists throughout the world have utilized the Rubin Test in the study of sterility, comparatively few records have been made of any untoward results. An occasional mishap has been noted but on investigation it has been found that the contraindications and technique for the test were not observed. In no instance was a serious accident encountered when carbon dioxide was used.

The importance of tubal patency in the etiology of sterility has been emphasized by accumulated experience with the Rubin Test. An analysis of 593 replies to a questionnaire sent out by Rubin (8) in 1939, gives an indication of the incidence of tubal obstruction. These replies tabulated 86,113 tests performed in this country and abroad, and revealed complete tubal obstruction in 30.88 per cent of the cases, and partial obstruction in 8.85 per cent. In Rubin's own cases numbering 5,269 insufflations up to 1940 the percentage of complete tubal obstructions was 32.4 per cent and of partial obstruction 33.1 per cent. These two groups of cases therefore show an almost similar incidence of obstructed tubes. It is in the cases of partially obstructed tubes that the two series reveal a difference. The explanation for this may be that the kymographic insufflation which Rubin uses gives more information and permits the diagnosis of partial obstruction in contradistinction to the results obtained with so-called simplified techniques.

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# THE FUNCTIONAL CAPACITY OF THE AGED

## ITS ESTIMATION AND PRACTICAL IMPORTANCE<sup>1</sup>

FREDERIC D. ZEMAN, M.D.<sup>2</sup>

(New York, N. Y.)

*"I have gout, asthma, and seven other maladies, but am otherwise very well."*

Sidney Smith (1771-1845)

### INTRODUCTION

That man has always been concerned with the prolongation of life and the alleviation of the ills of old age is clearly evident from the study of primitive cultures and folk-lore (1). The Romans believed that old age was itself a disease (*senectus ipsa est morbus*), and medical writers for many centuries thereafter recorded remedies for a great variety of senile complaints without having any understanding of the underlying causes. Only in the past hundred years with the development of modern medicine, which is based on the correlation of clinical and post-mortem observations, and is aided by methods of precise measurement, has it been possible to attempt the differentiation of the aging process, characteristic of all living matter, from the superimposed diseases occurring in the aged.

Clinical studies have abundantly demonstrated what has always been known to the man in the street: that the older one becomes the greater is the liability to disease, and the greater is the number of diseases that may be found in any one person. This multiplicity of lesions in the old is most confusing to the physician since it often makes both diagnosis and treatment most difficult. Careful clinical judgment is required to decide which one of several diseases is responsible for the patient's discomfort, and to determine upon a course of treatment which will combat this specific disease without affecting other parts of the body injuriously.

That many old people overcome their natural and acquired infirmities and carry on useful active lives, may be observed on every hand, and was especially evident during the war years. The chronological age of an individual may be most deceptive. Since some are old at forty years, while others are relatively young at seventy, we have long been aware of the importance of the functional capacity of the aged. This may be defined as the ability of an old man or woman to engage in purposeful activity, and is only indirectly related to the pathological lesions that may be found on physical examination. Description of the methods used in its measurement and the discussion of the many practical applications of a functional classification is the aim of this communication.

### HISTORICAL DEVELOPMENT

The students of heart disease were the first to realize that the customary medical diagnosis, which enumerates the abnormal conditions found upon careful

<sup>1</sup> From the Medical Service, Home for Aged and Infirm Hebrews, New York City.

<sup>2</sup> Presented in preliminary form, National Conference of Social Work, June 1945.

study of the patient, yields no direct information about the functional status of the individual. Thus, one might read on a chart the following: "chronic rheumatic valvular disease, mitral stenosis and aortic insufficiency"; and remain entirely in the dark as to whether the patient was able to be up and about, was confined to bed, or was able to indulge only in limited activity. For this reason, about twenty years ago the New York Heart Association adopted this classification of the functional capacity of cardiac patients.

"Class I—Patients with cardiac disease and *no limitation of physical activity*. Ordinary physical activity does not cause discomfort.

"Class II—Patients with cardiac diseases and *slight limitation of physical activity*. They are comfortable at rest but on ordinary physical exertion experience discomfort in the form of undue fatigue, palpitation, dyspnea or anginal pain.

"Class III—Patients with cardiac disease and *marked limitation of physical activity*. They are comfortable at rest, but the above symptoms are caused by less than ordinary activity.

"Class IV—Patients with cardiac disease who are *unable to carry on any physical activity without discomfort*. Symptoms of cardiac insufficiency, or of the anginal syndrome, are present, even at rest" (2). The decisions as to the place of a cardiac patient in this scheme are made by the physician after a careful study of the history and the physical findings. The addition of this information regarding function to the customary listing of diagnostic findings has proven to be of the greatest value and is in constant use in heart clinics all over the country.

The first published use of a functional classification for the aged is to be found in "A Study of the Medical Needs of Recipients of Old Age Assistance in New York City in 1934 (3), carried out by the Research Bureau of the Welfare Council of New York City in cooperation with the Department of Public Welfare and the New York State Department of Social Welfare. Emphasis was laid upon the necessity for distinguishing "among persons who have conditions that are diagnosed as disease, between those who are thereby incapacitated in various ways for normal living and those whose capacity for normal living is not seriously impaired". The examining physicians who carried out this investigation used the following categories of disability in rating each individual.

"1—No obvious disability; i.e., no condition found that interferes with ordinary activities.

2—Up and able to get about; i.e., not in Class 1, but able to be up and about, travel, to find recreation, and attend a clinic.

3—Homebound; i.e., not wholly confined to bed or chair, may be able to get out of doors in yard or block.

4—Bedridden, or if able to get out of bed, wholly confined to a chair."

This investigation disclosed that of 948 men and women, seventy years of age and over, 231 or 24.4 per cent showed no obvious disability; 505, or 53.3 per cent were able to be up and about; 165, or 17.4 per cent were homebound; and 47, or 4.9 per cent, bedridden. Of the first group, comprising 231 persons with no disability, 33 individuals were found entirely free from disease. The report



points out that "the discovery of these 33 persons lends support to the view that old age in itself, unaccompanied by actual pathological conditions, is not incapacitating." Of the remaining 198 in this group, all had one or more maladies diagnosed, but nevertheless had escaped disability. The conclusion is drawn that "old age and many of the milder forms of the diseases of the aged are not disabling in and of themselves."

The fallaciousness of many accepted clinical concepts of the relationship between disease and physical efficiency has been emphasized by Jokl in his studies of young athletes (4). One of his cases is particularly striking. "A Rugby player who died after a test game had a cystically degenerated right kidney the size of a walnut, a greatly hypertrophied left kidney, a much enlarged heart with a degenerated myocardium and thick prominent atheromatous patches in the coronary arteries and a hypoplastic abdominal aorta. There was a persistent thymus, in which microscopic examination revealed much active tissue. On account of his outstanding feats on the playing field the deceased had been called the 'iron man of South African Rugby football'." Such discrepancies between structure and function are commonly found in the aged, and every practicing physician has wondered how some of his older patients have kept actively at work in spite of obvious anatomic defects.

#### EXPERIENCE OF THE HOME FOR AGED AND INFIRM HEBREWS

Realization of the inadequacy of the usual medical diagnosis to give a complete picture of the condition of old people led us at the Home to develop our own functional classification, based on the foregoing examples, and adapted for use in an institution housing some 350 men and women over sixty years of age. We have added to the four major headings a fifth to include a specially handicapped group, the blind. The classification now in use, as modified in the course of ten years experience, is given herewith:

Class A—Individuals capable of unlimited and unsupervised activity, to be trusted to go about the city in safety.

Class B—Individuals capable of moderate activity, to be trusted in the neighborhood of home, but who may require for extended or tiring trips the escort of a younger person.

Class C—Individuals whose capabilities are limited and whose activities need both assistance and supervision; require escort on the street; practically housebound.

Class D—Individuals who are confined to bed or its immediate vicinity.

Class E—Individuals who are totally blind, or whose vision is so impaired that they cannot take care of themselves.

To this classification we have added a numerical designation of skills, largely for the guidance of the occupational therapy department but also useful for the administrative staff. Thus the numeral 1 indicates specialized skill, the numeral 2, ordinary skill, and 3, unskilled or handicapped in some way. In this fashion, the chart of each of our residents carries symbols which may seem cryptic to the uninitiated, but convey volumes of information to our workers. Thus, A1 indi-

icates an able-bodied person, who, if a man, may be a carpenter or a tailor, and, if a woman, may be an expert seamstress or a trained cook. The notation B3 indicates a partially handicapped person, with no particular skills.

This functional grouping attempts only to make gross differentiations. Within each group several subdivisions are possible and may be made in accordance with the personal judgment of the physician. The absence of exact methods of measurement precludes at present the possibility of setting up precise objective criteria (5).

The determination of the functional capacity of each resident of the Home is the task of the medical staff, and is based upon a careful history, a thorough physical examination, and special tests such as urine analysis, x-ray film of the heart and lungs, blood examination including the Wasserman reaction, measurement of the vital capacity of lungs and such other types of investigation as are indicated. The study of testing the functional capacity of younger individuals was greatly stimulated by the needs of the armed forces, and the reader is referred to original articles on this subject for more detailed information (6). For practical purposes, especially in work with older people, the information offered by the patient as to what he can or cannot do in the way of work or activity is often more helpful than specialized technical procedures. The need of contemplating each individual in his entirety and of giving full weight to many diverse factors frequently makes the physicians' task very difficult, particularly in those cases where the patient's own estimate is more liberal than that of the medical advisor. Such disagreements require the greatest tact on the part of the doctor. Psychological factors must be given careful consideration, since patients with mental peculiarities will often require careful supervision.

These functional ratings require periodic review since the capacities of the residents change from time to time, and over a period of years one individual may proceed downward in the scale as the result of specific diseases and increasing infirmity. Less commonly one sees patients whose functional capacities improve after admission to the institution to such an extent that their ratings must be revised upward. Such improvement may be observed in cases of marked nutritional deficiency (7). In institutions where periodic physical examinations are made annually, the opportunity is offered on these occasions for study of the functional status, and modifications of the ratings if necessary. In Table I we see the functional breakdown of the population of a large home for aged. As we would expect, 188, or more than one-half are in the C group. No particular sex differences are noted. In general there is increasing disability with advancing age.

#### THE UTILITY OF FUNCTIONAL RATINGS

The important uses of this method of estimating the ability of the aged may be discussed from the viewpoints of the physician, of the staffs of institutions, and of welfare agencies. Its application to the problems of industry will also be explored.

By requiring a decision on functional capacity the examining physician is forced to think in terms of the whole individual, rather than in terms of the

diagnosed diseases, the names of which are often more imposing than important. It is not at all uncommon to find on the face sheets of our clinical records an enumeration such as this: "hypertension; arteriosclerotic heart disease; sclerosis of coronary arteries, anginal syndrome; sclerosis of peripheral blood vessels. (legs); osteo-arthritis of hands, lumbar spine and knees; hemorrhoids; psoriasis." To many physicians, and certainly to most medical social workers this catalogue of maladies would indicate a seriously sick individual, and yet many of our

TABLE I

*General functional capacity of residents of Home for Aged and Infirm Hebrews, January 1, 1946*

AGE GROUPS	TOTAL		RATINGS				
	No.	%	A	B	C	D	E
60-64 years Male	4	1.09	1	1	2		
Female	9	2.48	1	5	1	2	
65-69 years Male	13	3.58	2	4	6	1	
Female	33	9.05	5	10	13	5	
70-74 years Male	40	10.97	6	15	16	3	
Female	41	11.20	6	12	17	6	
75-79 years Male	57	15.63	4	19	28	6	
Female	61	16.72	5	24	27	5	
80-84 years Male	27	7.39	1	6	17	3	
Female	42	11.52	1	4	31	5	1
85-89 years Male	17	4.67		1	15	1	
Female	15	4.10		1	10	4	
90-94 years Male	2	0.48			2		
Female	3	0.84			3		
95-99 years Male	0	0.00					
Female	1	0.28					1
Male	160	100%	14	46	86	14	0
Female	205		18	56	102	27	2
Total	365		32	102	188	41	2

Class B patients have all these diseases, often in association with diabetes mellitus. When the physician has arrived at a functional estimate, he is then in a position to advise as to the placement of the patient, the type of care needed and the amount of work that the patient should be allowed to do. It is becoming increasingly clear to those working in the field of the aged that Class A cases do not need institutional care, and are best cared for in the community, preferably in their own homes, or in boarding homes. Placement in an institution is usually required for three of the five groups. Obviously Class D cases need active medical and nursing care, whereas Class C and E cases may only require

the assistance of trained attendants in dressing and getting about from one part of the home to another.

The work prescription is a serious responsibility of the physician and is directly related to the functional diagnosis, rather than to the patient's own eagerness to run errands, work about the home, or spend more time in occupational therapy classes. We do not subscribe to the policy of *laissez-faire* in this matter advocated by some on the ground that anything that makes an old person happy is of itself a good thing. We believe rather that it is our duty to postpone as far as possible the inevitable cerebral hemorrhage, and to stave off the impending cardiac breakdown by the limitation of obviously harmful activity. Every now and then an obsessive compulsive type of resident forces us to compromise with our ideals in the interests of peace.

From the standpoint of the administrative staff of a home the functional rating has definite practical value. This is equally true of the social service and the occupational therapy departments, all of which are staffed by lay workers, to whom many of the medical diagnoses, although familiar, are difficult to interpret. The executive heads of institutions for the aged in these days of labor shortages are more and more forced to turn to their residents for help in the actual work of their small communities. It is far easier to fit old people to their tasks when an expert estimate of their capacity is at hand for guidance.

The Social Service Department of a modern home for the aged has at least three major functions; i.e., giving advice to applicants for admission and to their relatives, the investigation of prospective candidates for admission and the follow-up of these individuals when admitted to ensure that they adapt themselves successfully to the new way of life. In all of these activities the worker must know the medical status of the person under consideration, and here again the functional rating has useful application. As has been noted above, not all people require care in institutions. Certainly the best interests of the community are served by reserving these facilities for the sick and handicapped aged.

Today most of the progressive institutions for the aged have occupational therapy programs under the direction of trained directors. While any activity of an old person in an institution may be looked upon as "occupational therapy", and as a valuable part of the mental hygiene program, nevertheless this term has come to be limited to a variety of handicrafts adapted to the interests of both sexes, and often producing objects of utility for the institution or for sale. The head of the therapy department must be largely guided by the physician's functional rating in planning activities. For this purpose the numerical ratings of the patient's manual skills are particularly advantageous.

As the use of functional designations becomes more widespread, their practical value will become apparent to workers in family welfare agencies, in visiting housekeeper organizations and in state and municipal agencies caring for the aged. Medical diagnosis alone is not enough on which to base important decisions as to type of care needed, or the amount of financial assistance required, nor does it make clear whether the type of home surroundings are proper for the patient's needs.

## THE EMPLOYMENT OF AGED INDIVIDUALS

In 1942 Wharton described the work of the "Old Man's Department" in the Dodge Plant of the Chrysler Corporation where the capabilities of men handicapped by age or disability or both are utilized to the advantage of both the company and the men (8). The late Edsel Ford in an article entitled "Why We Employ Aged and Handicapped Workers", stated that of the workers employed in the River Rouge industrial area, more than 27 per cent were over fifty years of age, hundreds were over seventy and seven workers were in their eighties. The psychological advantages of keeping men gainfully employed are emphasized as a means of preventing the hopelessness so common in old men (9). The whole problem of "The Older Worker" (10) has been admirably presented by the distinguished physiologist, Dr. A. J. Carlson, who believes that by keeping older workers in idleness we are wasting valuable human resources, and contributing to the biologic deterioration of our society.

The lessons learned in the war years should not be forgotten in the days of peace to come. Workers past fifty and sixty years have a real and substantial contribution to make. Their employment will tend to keep them in better mental health and will serve to spare the nation huge burdens in the form of taxation for pensions. An enlightened attitude on the part of industry will serve society as a whole.

Recent publications have shown the growing interest on the part of physicians, especially those examining factory workers, in setting up standards and methods of studying the ability of special groups of the handicapped. Ritter (11) has studied "Hypertension in Industry," and set up a yardstick for judging employability in cases of elevated blood pressure. Poole and Bent (12) as well as Kresky and Goldwater (13) have studied the employment potentialities of cardiac patients, stressing the need for careful medical evaluation of each individual. Mosenthal (14) has urged greater opportunities for diabetics in industry. In a study of senescence and industrial efficiency Stieglitz (15) urges that in a program for utilizing the best mental and physical abilities of older age groups, executives as well as workers should have benefit of what he calls "individualized constructive medicine." He feels that "the maximum development of the tremendous potentialities of fully matured men will require cooperative efforts of the best skills of personnel management, of industrial medicine, of educators and of physicians particularly conversant with the problems of senescence."

In large plants with well organized medical departments there is but little chance of old people venturing beyond their depth in seeking employment. Those physically or mentally unfitted are screened out by the examiners. There are however many types of employment where no medical check-ups are made. The writer has, for example, in the past few years encountered many old men working as apartment house elevator operators who not only appeared feeble, but whose senile memory defects made it impossible for them to retain floor numbers for even a few seconds. It is clear that physical examinations and functional estimations will prevent these individuals from suffering humiliation and frustration.



The functional classification herewith presented as of use in institutional and family agency work with the aged has its application also in problems presented by industry. It will serve to weed out the unemployables, Class C, D and E, and will furnish the basis for judgment on the possibly employable persons in Classes A and B. Much reasearch has been done on the physical fitness of soldiers, and the possible application of these findings to the problems of the aged awaits future development. Certainly it should be possible to divide our Group A into several sub-divisions to indicate different grades of physical ability.

#### SUMMARY

A method of functional classification of the aged applicable to the needs of institutions and other social agencies, is described. The utility of this concept over a ten year period of trial has been emphasized, and its application to a variety of problems is discussed. Its use in determining the employability of individuals in factories and elsewhere is commented upon. Finally the suggestion is made that these methods and the underlying ideas should have wider application in practice among the aged in order that emphasis may be placed on physiologic rather than chronologic age.

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## MUCUS, SPERM, AND INFERTILITY

### STUDIES CONCERNING HUMAN CERVICAL MUCUS AND SPERM MIGRATION IN RELATION TO INFERTILITY

A. R. ABARBANEL, M.D.

(Los Angeles, Calif.)

*From the Department of Obstetrics and Gynecology, College of Medical Evangelists*

That the cyclic changes in the human endocervical secretions are under the hormonal control of the ovary has been presumed on the basis of much circumstantial evidence. This report demonstrates that these cyclic changes in the human cervical mucus can be artificially reproduced by means of estrogen and progesterone in bilaterally ovariectomized, hysterectomized women. Further, the significance of these cyclic changes for sperm migration through the cervical mucus have been correlated.

*Historical review.* Donné, in 1837, reported that the secretion on the surface of stratified squamous epithelium was always acid and that from a surface of columnar epithelium was alkaline. Thus, the vaginal secretions in reproductive life were acid, while the endocervical mucus was alkaline (1).

W. Tyler Smith, in his monograph on "Leucorrhea" published in 1855, was the first to report the cyclic changes in the cervical mucus, noting in particular that it was least thick and viscid in the week after the end of the menses (2). Further, Smith observed, since this is "the time impregnation is most likely to take place, and is also the time when the mucous contents of the cervix are in the most fluid condition, . . . and since the spermatozoa have to make their way through the plug of mucus, . . . it is a plain inference that this mucus must be adopted for the preservation and ascent of the spermatozoa to the cavity of the fundus uteri." (*italics mine*).

Eleven years later, J. Marion Sims published his book on "Uterine Surgery with Special Reference to the Sterile Condition" (3). Acknowledging the previous studies of W. Tyler Smith, Sims also reported on the role of the cervix in sterility. Amplifying this two years later, Sims (4a, b) very definitely pointed out the essential use of the microscope in determining whether the semen was adequate in relationship to the cervical mucus. About a week after the end of menses, his patients were told to have intercourse and then report 12 to 14 hours later. He then aspirated the vaginal contents with one syringe and, after wiping the vagina and external os with cotton, aspirated the lower cervical mucus, and then the portion from the level of the internal os. If actively motile spermatozoa were found in the upper cervical mucus 36-40 hours post-coition he exonerated the male as well as the cervix as factors in the infertility. He noted that the mucus at this time (some 6 days post menstrual) was clear and translucent while premenstrually it was thick and opaque.

The lone voice of Sims was again raised in 1888 on the importance of the post-coital test (4c). In 1913, however, Huhner redirected attention to this test and since then has repeatedly emphasized its importance (5). But it was not until

1933 that Seguy and Vimeaux (6) demonstrated the cyclic alterations in the cervical mucus and showed that between the tenth and fifteenth day of the menstrual cycle, especially the thirteenth to fifteenth day, the mucus very rapidly increased in volume, markedly decreased in viscosity, and only at this time was the mucus easily and rapidly penetrable by sperm. Seguy and Simonnet (7) found that at the time of these characteristic changes in the mucus there was an associated rise in urinary estrogen. By evidence secured at laparotomy, the secretion of this typical mid-cyclic mucus was felt to be a reliable sign of ovulation.

Further evidence of the stimulatory effect of estrogen was offered by Moricard in 1936, who showed that estradiol given to a bilaterally oophorectomized woman resulted in the secretion of clear watery cervical mucus (8). Numerous investigators since then have confirmed and extended this (9, 10, 11, 12 and 13). Shettles (12 and 13), in particular, showed that estrogen produced mucus easily and rapidly penetrable by sperm (*in vitro*).

Lamar and his co-workers extensively confirmed Seguy's findings by a very ingenious *in vitro* technique (14), finding that as a rule, the mucus was penetrable for only a few days during any one cycle, usually around the thirteenth to sixteenth days.

Sjovall, in 1939, published a series of extensive investigations to prove that the human endocervix underwent cyclic histological changes, the most intense proliferation occurring at mid cycle. Further, after reproducing the cyclic anatomical changes in the cervical glands and their secretions in spayed female guinea pigs by means of estrogen and progesterone, he concluded that estrogen was the essential factor in stimulating the secretion of the easily penetrable mucus for the ready migration of sperms under their own powers of motility (15).

*Materials and Methods.* In 1940, the author began his studies on sperm migration and cervical mucus under the guidance of Dr. I. C. Rubin. Normally menstruating women were studied in addition to seven castrates who had just a cervical "stump" left following surgery one to twenty years previously. Since then over fifty women have been intensively studied. Over 2500 tests of sperm migration have been carried out, both *in vivo* (post-coital) and *in vitro*. The latter has been by the method of Lamar (14). In addition, a modification of his technique was carried out to obviate the criticism that the bubble of air introduced extraneous factors. Capillary tubes were filled with as long a column of mucus as possible, usually 5 to 10 cm. Then a capillary tube smaller in outside diameter than the other was filled with fresh semen. The portion dipped into the semen was broken off and then the end of the tube was introduced carefully into the larger one with the mucus. In addition, correlational post-coital studies on sperm migration in cervical mucus were made upon several score of women in conjunction with the basal body temperature curves and endometrial biopsies (taken on the first day of flow).

The estrogens utilized were estradiol benzoate and dipropionate, estrone, diethylstilbestrol, hexestrol and dinestrol. The progestogens used were progesterone and ethinyl testosterone (anhydro-oxy-progesterone). In addition a few studies were made with methyl testosterone and testosterone propionate.

## RESULTS

I. *Cyclic changes in normal cycle* (fig. 1).

a. *Post-menstrual phase* (days 5–10 of cycle). The volume is scant to moderate, while the mucus is opalescent and somewhat gelatinous with a two-to-three plus viscosity. Leucocytes are present in moderate numbers. Sperm may infrequently penetrate for a short distance but soon become immotile.

b. *Pre-ovulatory phase of late proliferative phase* (days 10–14 of cycle). Beginning about the tenth or eleventh day of the cycle, a series of changes in the mucus take place with increasingly rapid crescendo reaching their acme about the fourteenth day, coinciding with the low point of the basal body temperature (hereafter designated as B.B.T.) curve, i.e. the day of the so-called "ovulatory dip" or temperature shift. The volume increases from two to as much as ten fold. Conversely, the viscosity markedly decreases. The mucus becomes clear, glairy, translucent, almost watery. Leucocytes disappear. Sperm now easily, rapidly and in relatively large numbers penetrate and migrate through the mucus. *In vitro*, sperm may remain actively motile (2–4 mm./min.) for 24 to 72 hours in this mucus. This is the only time of the cycle that this occurs. Interestingly, only a relatively small number of sperm actually do penetrate, perhaps about one per cent. Grossly abnormal sperm (heads) may also migrate into the mucus.

c. *Post-ovulatory phase* (luteal or secretory phase—days 16 to 28–30). As a rule within 48 to 72 hours the volume decreases markedly until by the nineteenth day or so it is very scant. In contrast, the viscosity quickly increases. Leucocytes reappear in a short time. Sperm, at first, may penetrate the mucus for a short distance but do not long remain motile. By the nineteenth day, (5 days after the temperature shift), they no longer can invade the mucus even if placed in direct contact for 24 to 48 hours. This state of affairs continues until menstruation.

Occasionally, a case was found in which the change from mid-cycle mucus was rather gradual so that sperm penetrated in decreasing numbers and remained motile for shorter periods of time over the course of a week or more. In such cases, the B.B.T. curve was irregular, indicating an increased supply of estrogen or a deficient corpus luteum. Where an endometrial biopsy was secured, an immature progesterational endometrium was usually found on the first day of flow.

d. *Menstrual fluid* was easily and rapidly penetrated. Sperm remained actively motile for 24 to 48 hours in it.

e. *pH* of the endocervical mucus was always found to be alkaline to nitrazine.

II. *Artificial reproduction of the cyclic changes in the cervical mucus* was accomplished in suitable hysterectomized, bilaterally ovariectomized women who had an apparently normal cervical stump (fig. 2).

a. *Proliferative or estrogenic phase*. By means of estradiol or estrone parenterally, or diethylstilbestrol or hexestrol orally, the changes in the cervical mucus characteristic of the pre-ovulatory phase at mid-cycle were reproduced. In practically all of these women, (who were from one to twenty years postoperative and who had not received any hormonal therapy for at least 3 months) the

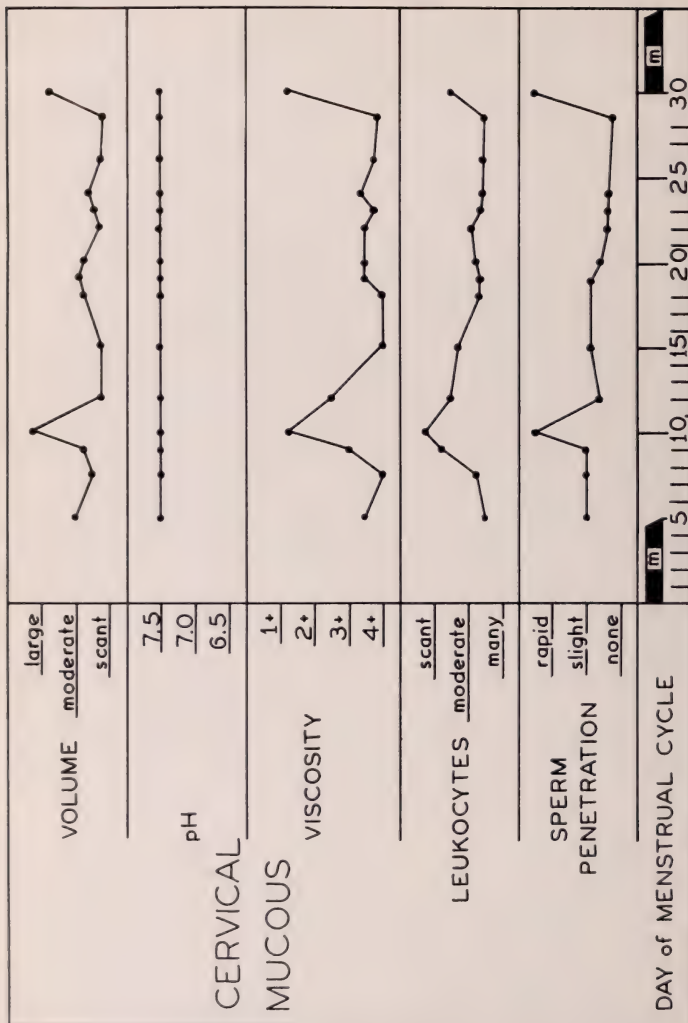


FIG. 1. Cyclic alterations in human cervical mucus and their relationships to sperm migration. In this particular woman, the so called "ovulatory dip" or temperature shift occurred on the eleventh day of the cycle. It should be noted in particular that on the tenth day of this cycle, the cervical mucus had reached its greatest volume, while viscosity was at its lowest. Sperm



control mucus was found to be extremely scant or absent. If present, it was a very scant crumbly material with much cellular debris. Dramatic, indeed, was the change after a suitably active estrogen had been given for a few days. Clear, albeit somewhat viscid mucus began to stream from the cervix. As a rule, about 5 to 14 days were required for a large volume of watery, clear, leucocyte-free mucus which sperm quickly and easily invaded, remaining motile in it for 1 to 3 days. In one woman, only 0.1 mg. of diethylstilbestrol daily for 3 days was necessary to stimulate the flow of clear mucus. In another, the cervix began to secrete mucus 36 hours after the insertion of a vaginal suppository containing 0.5 mg. of diethylstilbestrol.

Progesterone, in doses up to 30 mg. a week, did not have any effect when used before any estrogen was given. Similar results were obtained with oral ethinyl testosterone (10 mg. daily for 15 days).

In one or two cases, it seemed as if testosterone propionate (100 mg. over a period of 2 weeks) did stimulate the secretion of a very small amount of opalescent, viscid mucus. But the results in the others were essentially negative. Similarly, negative findings were noted with oral methyl testosterone (10 mg. daily for 15 days).

b. *Post-ovulatory or luteal phase.* After a clear, watery mucus, easily penetrable by sperm, had been produced by means of estrogen, the latter was continued while, in addition, progestogens (progesterone or ethinyl testosterone) were administered. In suitable dosage, the changes previously described (v.s.) as characteristic of the second half of the cycle were reproduced. Briefly, the volume decreased, the viscosity rapidly increased, leucocytes again appeared, while sperm soon were no longer able to penetrate. For the first few days, however, after progestogens were started, sperm would occasionally penetrate, especially if the dosage were small. As a matter of fact, in two instances for some 3 to 5 days, the sperm actually seemed to do better as regards penetration and duration of motility. If the amount of progestogen was sufficiently great, however, there was no doubt of the very sharp and dramatic changes brought about. As a rule, it required from 5 to 10 mg. of progesterone to overcome the effects of 0.5 to 1 mg. of estradiol, although occasionally up to 20 mg. was necessary. Ethinyl testosterone had to be given in daily oral doses of 20 to 60 mg. to produce the same effect. Neither testosterone propionate (100 mg.) nor oral methyl testosterone (150 mg.) was effective in changing the character of the mucus.

*Discussion.* Clearly, the evidence developed by these studies prove that the biological and physicochemical properties of the cervical mucus in the human are under the hormonal control of the ovary, since the cyclic changes observed in normally menstruating women were reproduced by means of estrogen alone and in combination with progestogen administered to suitable castrates.

Correlation of the available data reveals that in the immediate pre-ovulatory phase there is a relatively rapid increase in the amount of biologically active and available estrogen (17 and 18). As a consequence, the cervical mucus increases markedly in volume, while its viscosity becomes remarkably diminished. Almost

invariably the volume and viscosity bear a direct *inverse* relationship to each other. On the other hand, when viscosity is least, sperm migration is greatest in

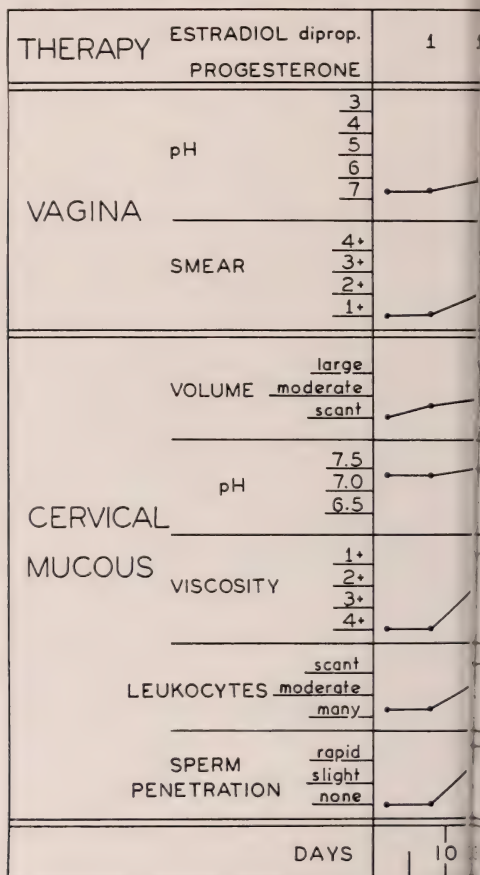
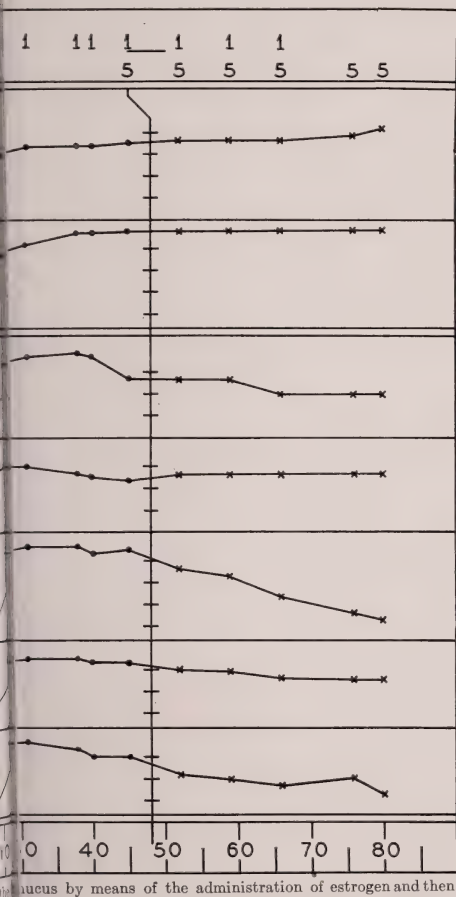


FIG. 2. Artificial reproduction of the cyclic changes in the progesterone to a suitable castrate in possession of just a "stump"

number, ease of penetration and duration of motility in the mucus. Unpublished data (19) show that the principal reason for the increase in volume with

the associated decrease in viscosity is primarily brought about by the amount of fluid, probably water (16), held in solution by the mucus. One of the factors



in this inhibition of fluid by the mucus may be an increased secretion of glycoprotein by the endocervix stimulated by the unopposed action of estrogen (19).

Even in pregnancy, the rubbery consistency of the cervical mucus may be changed to that characteristic of the mid-cycle by means of very large doses of diethylstilbestrol (19).

In summary, then, the essential physiological role of the estrogen-induced pre-ovulatory changes in the cervical mucus is to provide, as W. Tyler Smith stated in 1855 (2), "a suitable medium for the passage of spermatozoa through the cervix uteri into the uterine cavity."

Clinically, several practical points become apparent:

1. *Post-coital examination of cervical mucus (Smith-Sims-Huhner test).* During the course of evaluating the infertile couple, a post coital examination should be routinely done as recommended by the American Society for the Study of Sterility. From the data presented, this test should be carried out within 24 hours of the "ovulatory dip" in the basal body temperature curve in order to be of utmost significance. For practical purposes, it is suggested that it be done on the 13th or 14th day of a 28 to 30 day cycle. As a matter of fact, we carry it out on at least two occasions during the month. We start on the 11th day, repeat again on the 14th day, and if necessary, on the 17th day, since in many women the time of the temperature shift may vary considerably.

2. *Endocervicitis.* Considerable study of sperm migration both *in vivo* and *in vitro* in mucus secreted from an infected cervix discloses that penetration is all too frequently either poor or absent, primarily because the mucus has an increased viscosity, even at mid-cycle. Leucocytes, even in clumps, do not impede sperm migration. Infection, however, results in a loss of fluid with a resultant increased viscosity and consequent decreased or absent sperm penetration. Obviously, clearing up the infection will bring about a normal state of affairs. If the cautery is used, great care must be exercised not to "cone" out too much tissue nor to leave a stenotic canal.

*Summary and conclusions.* The human endocervical secretions undergo cyclic changes which have been proven to be clearly under the control of the ovarian hormones because the cyclic alterations in the mucus have been entirely duplicated in suitably castrated women by means of various estrogens alone and in combination with various progestogens.

In the immediate pre-ovulatory phase (about days 13 to 15 of an average 28 to 30 day cycle), and synchronous with the so-called "ovulatory dip" or temperature shift in the basal body temperature curve, there occur the following characteristic changes in the cervical mucus: a decided increase in volume, a marked decrease in viscosity, and practically complete absence of polymorphonuclear leucocytes. This clear, watery mucus is easily and rapidly penetrable by relatively large numbers of sperm which remain actively motile in it for 24 to 72 hours—a longer time by far than in mucus obtained at any other time of the cycle! These conditions prevail for only about 1 to 3 days in the average woman's cycle.

These alterations in the cervical mucus, characteristic of the immediate pre-ovulatory phase of the cycle, were entirely duplicated in suitable women castrates (with just a stump of cervix remaining), by the administration of various estrogens, including estradiol and diethylstilbestrol.

In control castrates progesterone alone, as well as testosterone propionate and methyl testosterone, in the dosage used, were not observed to stimulate the flow of cervical mucus.

An essential factor in the increase of the volume of the cervical mucus along with the concomitant decrease in viscosity appears to be an increase in the relative amount of fluid (water?) in the cervical secretions. Sperm penetration and migration were maximal when viscosity was minimal. As a rule, viscosity and volume were inversely proportional.

Following ovulation and with establishment of the post-ovulatory rise in the basal body temperature curve, the volume markedly decreases, the viscosity rapidly increases, leucocytes once more are noted, while sperm no longer are able to invade the mucus even though they remain actively motile for 24 to 48 hours. These post-ovulatory changes were completely reproduced in estrogen-primed castrates by means of either of two active progestogens—progesterone and ethinyl testosterone.

In the light of these observations, post coital studies of sperm migration into the cervical mucus can be of utmost significance only when made in the immediate pre-ovulatory phase of the cycle, i.e., within 24 hours of the so-called "ovulatory dip" or temperature shift in the basal body temperature curve. For adequate clinical evaluation, this test should be performed on about day 11 repeated on day 14 and if necessary on day 17 of an average 26 to 30 day cycle.

Chronic infection of the endocervix, with or without concomitant erosion, brings about an increased viscosity of the cervical mucus. As a result, infertility may follow because of the hindrance to normal sperm migration.

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## PRESENT STATUS OF HYSTEROSALPINGOGRAPHY

ARTHUR J. BENDICK, M.D.

(*New York, N. Y.*)

An anniversary volume dedicated to Dr. Rubin would be incomplete without an article on the subject of the x-ray studies of the female generative tract. He was a pioneer in this work and a large part of his activities was devoted to the study of sterility in women and hysterosalpingography plays a very important part in this work.

As far back as 1914, Carey used collargol injected into the Fallopian tubes to determine tubal patency. Dr. Rubin soon followed with some of his own work, but it was not until 1920 that he conceived the use of tubal insufflation in the study of tubal patency. Soon after this, I became associated with him in some of this work and attached the manometer to the insufflation apparatus so that the pressure could be accurately determined.

A great impetus was given to this work by the introduction by Sicard and Forestier in 1922 of the use of lipiodol. Dr. Rubin and myself published two papers on the use of lipiodol in 1926 and 1928.

Since then, many thousands of cases have been examined all over the world and the value of hysterosalpingography has been proven and is now accepted as a routine test. No one questions its value, but the procedure still varies with different men and there is still need of some improvement, especially in the opaque media, all at present having some objections. Having used most of the different media, I believe a short résumé of the test and its limitations and uses would be in order.

The test can be performed in any hospital or private office—in fact, I have used it in hundreds of office cases, allowing the patients to go home an hour after the test.

The apparatus needed is very simple. A uterine cannula and syringe, sponge holder, tenaculum and vaginal speculum are required. After inserting the speculum, the external os is painted with tincture of iodine. The cervix is then gripped with a tenaculum and the cannula is inserted. The procedure then varies with different workers. Some prefer fluoroscopic control, others simply inject blindly, depending on successive plates with measured amounts.

I have always used fluoroscopic control of the injection with successive spot films as the fluid is slowly injected and fills the uterine cavity and then the tubes. When the tubes are filled, the injection is stopped, the cannula removed and several films taken on the Bucky diaphragm as the uterus expels the opaque material.

Various opaque media are now in use of which lipiodol is the most common. It has the advantage of casting an extremely dense shadow, clearly outlining the tubes. The fluid is not irritating even when in the peritoneal cavity. It has the disadvantage of remaining in the tubes and peritoneal cavity for many years and may cause subsequent errors in diagnosis.

When the urologists developed chemicals for excretion pyelography, they were also tried for tubal studies. Of these diodrast thickened with acacia was the most popular. It had the advantage of rapid absorption, most of it disappearing in a half hour. The density of the shadow and consequently the detail was not as good as with lipiodol and further diodrast was slightly irritating when it passed into the peritoneal cavity.

In 1941, Rubin and his co-workers developed Rayopake. This is a water soluble opaque material with the chemical formula of Diethanolamine salt of 2,4-dioxo-3-iodo-6-methyl tetrahydro-pyridine acetic acid. It absorbs rapidly and completely, gives a dense shadow and has many advantages over diodrast. A small amount can be used to coat the uterine surface, and gives a mucosal pattern similar to that in the x-ray study of the stomach and intestines. As little as 2.0 cc. will often give a very satisfactory film. Rayopake has, however, the disadvantage of being irritating when it reaches the peritoneal cavity and causes symptoms of severe peritoneal irritation.

I believe that manometers to control the pressure are not necessary. In 1928, I devised a small bulb attached to a Tycos manometer painted with radium. With this I was able to control the pressure during the fluoroscopic examination. I have now given this up completely. I believe the use of large mercury manometers are not only unnecessary, but increase the hazards of the test. With all the media now in use, it is important to use as little as possible. When a manometer is used, air pressure is built up in the bulb and air spaces. If there is a relaxation of a spasm or an obstruction is overcome, too much fluid is forced into the uterus. This does not occur with a glass syringe connected directly to the cannula. I know of no urologist who now uses a manometer for pyelograms or cystograms. With a little experience, one senses just how much pressure can be exerted on the syringe. This method is simple and direct and has proven adequate in thousands of cases.

It is more difficult to decide what opaque material to use. As stated above, none of the media are perfect. Personally I use the following procedure.

If the examination is made because of sterility, exact information is needed as to the condition of both Fallopian tubes. For these cases I use lipiodol. Working under fluoroscopic control, a minimal amount is used. Four cc. may be enough, but as much as 10.0 cc. may be given. If the tubes are closed at the uterine end, no harm can result and all can be left in. If some is seen entering the tubes, the residue in the uterus can be withdrawn again under fluoroscopic control. With this method only a small amount can enter the peritoneal cavity. For this type of patient, lipiodol is required because of the importance of an 18 to 24 hour film. If a tube is stenosed but not completely blocked, the lipiodol can be demonstrated in the peritoneal cavity by a film taken the following morning. If diodrast or rayopake is used, this late film is useless, as the material has all been absorbed. Yet women with these stenosed tubes may become pregnant and the correct diagnosis can only be made if lipiodol is used.

If the examination is made solely for the study of the uterus, I prefer rayopake.

This material coats the wall better than lipiodol, and will outline small polyps and hyperplasia better than the other media. After the film has been taken, it can be withdrawn and a syringe of air injected and excellent double contrast films can be obtained. The uterine coating is often improved by the contrast with the air and the increased expansion of the cavity. Rayopake has the disadvantage of being irritating in the peritoneal cavity. To prevent this, most workers try to use only small quantities—often only 2.0 cc. but this amount is often too small. Even with this small amount, uterine contraction can force the media out through normal tubes into the peritoneal cavity. Two of my patients showed evidence of peritoneal shock. They complained of extreme abdominal pain and went into collapse. Both recovered completely in a few hours.

I believe the ideal media is yet to be developed. It must be non-irritating, cast a dense shadow, absorb slowly so that it can be visualized for several days and then slowly disappear.

The question is often asked, "How does hysterosalpingography compare with tubal insufflation?" I believe each test supplements but does not supplant the other. Air insufflation is rapid, inexpensive, and gives immediate information if at least one tube is patent. With more complicated apparatus, the expert can also tell if the tube is partially blocked or spastic. Hystero-grams, however, tell not only if the tube is blocked, but locate the obstruction at the fimbria or uterine end. They also give information as to the condition of the tube, if it is dilated or narrowed, capable of peristalsis or atonic, or if the uterus is the cause of the sterility. Lastly, the information obtained from the hystero-gram is so definite that only a minimal amount of training is required for its interpretation.

Surgeons differ as to what type of diseased tube is most favorable for operations to correct sterility. Some believe that if the tube is closed at the fimbria, the case is most favorable for operation. They contend that merely freeing the fimbria from the adhesions is all that is necessary. Other surgeons believe that the desirable cases are those in which the tubes are occluded at the uterine end. They maintain that a fertilized ovum cannot pass through a dilated infected tube which has lost its peristalsis. I hold no brief for either school and do not know which is correct, but hystero-grams will allow the surgeon to pick the type case that he believes is the most favorable. I do not believe any woman should be operated on for sterility without first having been examined by hysterosalpingography.

Does hysterosalpingography ever cause sterility? I do not think so. I know of two cases of pregnancy in women previously sterile in which conception followed shortly after the test. A properly controlled test is an aid and not a barrier to pregnancy.

The test is also of great value in the study of the abnormal uterus. The size and position of the organ is accurately demonstrated. Are there fibroids, and if so, submucous or intramural? Single or multiple? Can the uterus be saved or is a hysterectomy necessary? I recently reported a case where two

capable gynecologists examined a case. One reported an enlarged uterus with a small mass interpreted as an ovary, the other considered the case to have a normal uterus with an enlarged ovary and tube. Clinically the case was one of an arrested pregnancy. Hystero-grams showed a normal uterus but a dead fetus, in the ampulla of the one tube. I do not believe the test should be made if a living fetus is present because of the danger of inducing an abortion. The test has been used for early diagnosis of pregnancy, but I believe it is contraindicated for this purpose as we now have simpler and safer procedures such as the Aschheim-Zondek test.

Is the test safe? Yes. There is no test which if applied to many thousands of cases will not occasionally have a bad result. I have had two cases where the lipiodol entered the venous system and was so demonstrated on the films. Yet neither of these two cases had any bad results. I believe the danger of air embolism is greater in tubal insufflation than from oil embolism in hystero-salpingography. Some cases complain of peritoneal irritation. The danger of carrying infection into the peritoneum is, I believe, over-emphasized. An infected tube is blocked, otherwise the patient would have peritonitis with clinical symptoms contraindicating the test.

The test is also of great value in differentiating between benign and malignant tumors. This may save the necessity of pre-operative diagnostic curettage. Some surgeons believe the curettage must be first performed and is fraught with little danger. Having seen lipiodol enter the venous system from the trauma of a blunt cannula, I cannot agree that the opening of hundreds of venous channels by the curette does not incur the danger of transmitting tumor cells into the venous system.

I believe that a better opaque medium will be developed and that periodic injections will be made under fluoroscopic control in order to overcome sterility. Enough cases have been reported of pregnancy following the test that excellent results can be expected in selected cases.

In closing, I would like to stress my belief that a hystero-gram is as harmless as a pyelogram and that the information it gives is just as important. In cases of sterility, it is often life-giving and in cases of neoplastic disease, it can be life-saving.



# HYPOTHYROIDISM IN FUNCTIONAL GYNECOLOGIC DISORDERS: WITHDRAWAL OF THYROID MEDICATION AS A DIAGNOSTIC AID

BERNARD BERGLAS, M.D.

(New York, N. Y.)

*From the Endocrine Clinic of the Gynecological Service and the Department  
of Laboratories, the Mount Sinai Hospital*

Hyposecretion of the thyroid gland, either as a primary or as a secondary etiologic factor, is found in a variety of clinical conditions. Its clinical manifestations depend upon the age of the patient and the degree of thyroid deficiency. Cretinism and myxedema, because of their definite clinical signs, generally present no such diagnostic difficulties as may be encountered in mild hypothyroidism. The manifestations of thyroid deficiency in childhood, such as retarded growth, delayed ossification of epiphyseal cartilages, or retarded eruption of teeth, are readily recognized and evaluated. In hypothyroidism which occurs later in life, after the mature skeletal characteristics have already developed, functional changes such as mental and physical sluggishness, amenorrhea, oligomenorrhea, or menometrorrhagia, sterility, or habitual abortion may form the clinical picture.

In view of the fact that the severity of the clinical signs is determined by the degree of thyroid deficiency and the length of time that it has prevailed, and since the signs are often not uniform and not definitely referable to a thyroid deficiency, the diagnosis of hypothyroidism often depends on functional tests—determination of basal metabolic rate and study of blood chemistry. The former is the commonly accepted measure of thyroid activity. The difficulties in obtaining basal conditions, especially in clinic patients, and possible errors in estimating deviations from standards as influenced by body weight and configuration, impose limitations upon the clinical evaluation of the basal metabolic rate.

Blood cholesterol values are also a useful aid in establishing a diagnosis of hypothyroidism. Luden in 1917 and Epstein and Lande in 1922, were the first to find a definite relationship between the basal metabolic rate and the blood cholesterol level in thyroid disease. It has since been shown that this level changes with the activity of the thyroid gland, and that the cholesterol concentration is in inverse relation to the basal metabolic rate. These findings have suggested the use of blood cholesterol values as a measure of the activity of the thyroid gland and as a corroborative test of the basal metabolic rate. The further demonstration (Luden; Mason, Hunt and Hurxthal) that administration of thyroid extract to hypothyroid patients causes a drop in blood cholesterol concentration makes it possible to measure the response of such patients to thyroid therapy by the resulting decrease in blood cholesterol values.

Nevertheless, the wide normal range and the spontaneous fluctuations of blood cholesterol concentration restrict the clinical application of cholesterol findings

for diagnosing hypothyroidism or for measuring efficacy of treatment in thyroid deficiency. In normal adults McGee found the serum cholesterol to range between 155 and 228 milligrams per 100 cc., with an average of 193; other reports (Sperry: Page) give values ranging from 132 to 392 milligrams per 100 cc., and from 109 to 376 milligrams per 100 cc., respectively. In 80 per cent of a group of normal children, Wilkins, Fleischmann, and Block found cholesterol values between 125 and 225 milligrams per 100 cc., while in the remaining 20 per cent the values ranged from 98 to 308 milligrams per 100 cc. The same authors report the range of cholesterol concentration in hypothyroid children as 145 to 660 milligrams per 100 cc., and a study by Mason, Hunt, and Hurxthal in hypothyroid adults disclosed a range of serum cholesterol between 217 and 500 milligrams per 100 cc.

Animal experiments have shown that the serum cholesterol concentration in thyroidectomized rabbits is subject to individual fluctuations of as much as 224 milligrams per 100 cc., while in the normal rabbit this fluctuation amounted to only 34 milligrams per 100 cc. (Fleischmann, Shumaker, and Wilkins). These experimental findings are in accord with our knowledge as to the spontaneous fluctuations of cholesterol concentration in man. Thus, Schube found that the level in normal adults fluctuated as much as 73 milligrams per 100 cc., and Wilkins *et al.* report spontaneous fluctuations in normal children amounting to 83 milligrams per 100 cc. In hypothyroid patients these fluctuations are considerably greater.

Important as average values are for statistical evaluation, the obvious overlapping of blood cholesterol concentrations in normal and hypothyroid individuals necessitates caution in the application of these data in any given instance. A high cholesterol concentration, in the absence of such conditions as nephrosis, diabetes, or liver disease, suggests a thyroid deficiency, although its absence does not necessarily rule out the possibility of hypothyroidism, since cholesterol values within the normal range in hypothyroid patients may represent levels considerably in excess of their normal values. Furthermore, because of the occurrence of spontaneous fluctuations, it is essential that repeated determinations of blood cholesterol concentration be carried out, as a guard against errors in diagnosis.

Several workers (Bronstein; Goodkind and Higgins; Hess) have observed that in hypothyroid children the serum cholesterol level rose considerably within one to three months after thyroid therapy was discontinued, and that the levels were higher than those prior to treatment. These observations have recently been confirmed in extensive studies carried out by Wilkins and Fleischmann. They found that within 4 to 20 weeks after cessation of thyroid medication of hypothyroid children the serum cholesterol values increased by 98 to 411 milligrams per 100 cc. as compared to the values found before treatment. In a control group of normal children, withdrawal of thyroid medication resulted in an increase of only 10 to 55 milligrams per 100 cc.; in other words, the serum cholesterol concentrations remained within the normal range of spontaneous fluctuations.

Thyroid deficiency plays an important role in adult women with functional

gynecologic disorders. Determinations of basal metabolic rate and serum cholesterol concentration are often unsatisfactory, especially when the thyroid deficiency is mild, as the values remain within the normal range. In some instances in which the presence of hypothyroidism is suspected from the clinical symptoms, although the laboratory findings are normal, the response to trial medication with thyroid extract will sometimes establish the diagnosis of hypothyroidism. The latest aid to diagnosing hypothyroidism—increased cholesterol values following cessation of thyroid therapy—has now been tested in a group of patients with clinically manifest or masked hypothyroidism. The two case histories which follow may serve as an example of the group of 11 thus far studied.

#### ILLUSTRATIVE CASES

*Case 1.* (#44-673) M. B.; 30 years old; chief complaint was oligomenorrhea. The previous medical and surgical histories were negative. The menarche began at 13, followed by regular menses with normal flow. At the age of 19 the menses became irregular, occurring at intervals of 1 to 4 months, lasting 1 to 3 days, and scanty in flow. At this time patient noted a tendency to obesity and hirsutism. In the past few years these signs and symptoms became more pronounced. The gynecologic findings were essentially normal. The blood count, sugar tolerance test, x-ray of sella turcica, examination of the fundi, androgen and estrogen determinations were all normal. The basal metabolic rate was minus 20 per cent, the serum cholesterol was 360 milligrams per 100 cc. The patient was put on thyroid extract, the dosage being gradually increased to 4 grains per day. While under this treatment, the menses became regular and the flow normal; the serum cholesterol fell to 250 milligrams per 100 cc. Thyroid medication was stopped; 6 weeks later the serum cholesterol had risen to 700 milligrams per 100 cc.

*Case 2.* (#45-2120) C. V.; 15½ years old; the only complaint was a delay in the onset of her menses. The general physical and gynecologic findings were normal. The routine laboratory examinations yielded normal results. The basal metabolic rate was plus 11 per cent, the serum cholesterol was 280 milligrams per 100 cc. The patient was put on thyroid extract, 2 grains per day. Three months later the patient began to menstruate, and the following menses continued normally. While on thyroid treatment, the serum cholesterol fell to 240 milligrams per 100 cc. Thyroid medication was stopped; 2 weeks later the serum cholesterol had risen to 540 milligrams per 100 cc.

#### DISCUSSION

In adults, functional disorders such as primary or secondary amenorrhea, oligomenorrhea, menometrorrhagia, sterility, or habitual abortion, may be the only clinical manifestations of hypothyroidism. Such cases respond readily to thyroid therapy, but the etiologic basis is apt not to be recognized. The basal metabolic rate and serum cholesterol concentration should, therefore, always be determined. The presence of hypothyroidism is not necessarily excluded by a basal metabolic rate and a cholesterol level within normal range. If, however, withdrawal of thyroid medication is followed by a considerable increase of blood cholesterol concentration, deficient activity of the thyroid gland may be presumed. While the basal metabolic rate is known to be low in pituitary deficiency and adrenal disease, the cholesterol levels are as a rule within normal limits. In such cases withdrawal of trial thyroid medication may not be followed by a rise in blood cholesterol concentration.

## SUMMARY

1. The diagnostic value of hypercholesteremia in hypothyroidism is discussed.
2. Two cases with functional gynecologic disorders due to hypothyroidism are presented. After withdrawal of thyroid medication an increase of serum cholesterol above the initial values was observed.
3. Results of the withdrawal of test medication with thyroid extract are presented as an aid in diagnosing hypothyroidism in functional gynecologic disorders.

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## GOUT IN EARLY LIFE

OLON S. BERNSTEIN, M.D.

(*New York, N. Y.*)

There is widespread belief that gout is a malady limited to the middle and later years of life. This opinion has been firmly held by both laity and physicians. From antiquity until the present day the unhappy victim of gout has been the frequent subject of caricature in art, literature and the theatre. The traditional picture is that of an elderly, obese, florid and usually affluent gentleman, whose years have been largely devoted to the pleasures of the table and the bottle. Analysis of several large series of cases would tend to dispute this conception. The average age at onset reported by Monroe (1) is 39, Kinell and Haden (2) 43.5, Brøchner-Mortensen (3) 47.7, Talbott (4) 32, Williamson (5) 38 and McCracken et al (6) 46.8. Of Williamson's (5) patients, 66 per cent were between 30 and 50 years of age, 50 per cent of Sherwood's (7) were between 31 and 50, 58 per cent of Brøchner-Mortensen's (3) between 18 and 50, and 65 per cent of McCracken's et al (6) between 19 and 50.

As evidence of the common lack of familiarity with the simple clinical picture of gout, an average period of ten years has been found to elapse between the initial appearance of symptoms and the establishment of the correct diagnosis (5, 6 and 8). This "shame of the physicians" (9) tends to persist despite repeated attempts of students of the disease (6 and 10) to create "gout consciousness." Although some English observers speak of its diminishing incidence (11), there are many spas, chiefly on the continent, where about 1 to 2 per cent of all treated patients are sufferers from gout (12). At the Mayo Clinic, patients with gout constitute at least 5 per cent of those seen by consultants on diseases of the joints. A similar incidence has been found at the Cleveland Clinic (2). Hench (13) believes that it is the suspicion of gout and not the disease itself that has disappeared.

Despite the recognition that the inherent character of gout is present at birth (14), the disorder is rarely encountered in the very young. The relative exemption of youth has not been adequately explained. The first circumstantial hint that gout may attack young individuals appears in the writings of Aretaeus (15) in the second century A. D. who cites the instance of a sufferer from gout who, between attacks, was able to win a Marathon race. The reference is interesting in that it stresses the completeness of the remissions. Hippocrates (16) has a relevant aphorism: "Puer non laborat podagra ante veneris usum." Sydenham, whose 17th century treatise on gout still remains the best description of the clinical features of the disease (17) remarks "I have not hitherto found children or very young persons affected with the true gout." Heberden (18) never knew a certain case before puberty.

### HEREDITY IN GOUT

It is quite generally agreed that gout is the result of an inherent metabolic error with a strong hereditary taint. Llewellyn (14), an English authority on



the disease, believes that it is an hereditary disorder but whether purely so or capable of acquisition *de novo*, he is not certain. Of all arthritic diseases gout furnishes by far the greater number of instances in which parents and children are alike affected. Garrod (19), who in 1847 was the first to demonstrate that abnormal amounts of uric acid could be recovered from patients suffering with gout, found the "ancestral trait" present in from 75 to 81 per cent of a large series. He believed that *de novo* acquisition had never been proved and that "breed is stronger than pasture." Most observers feel that it is not gout but a predisposition thereto that is inherited. This involves inborn tissue potentiality in the absence of which the predisposing or exciting causes are unable to provoke the disease. Thus gout may remain quiescent throughout life.

Figures on the incidence of heredity in gout vary widely, some authors (2, 5, 13 and 20) stressing the low, others (19 and 21) the high occurrence. In England in three large series the percentage incidence varies from 38 to 81 (14, 19 and 22). In America, on the other hand, the percentage of patients giving an hereditary history varies from 7 to 18 (5, 6 and 13). This striking difference may be explained by the fact that American family records are not as complete as those in England. The frequency with which an affirmative history of hereditary gout may be elicited will depend largely upon the diligence and thoroughness of the medical and social investigation (4). Pursuing such painstaking methods familial figures as high as 75 per cent have been obtained (23). Of considerable significance in supporting the belief that gout is almost always an hereditary disease is the frequent discovery of hyperuricemia in the symptomless kin of gouty individuals (4 and 24). Jacobson (25) determined the serum uric acid in the son of each of two gouty individuals and in the mother of a third. These relatives were clinically free from gout, but their uric acid concentrations were 6.7, 7.7 and 8 mg. per cent respectively. Talbott (4) also found hyperuricemia in 25 per cent of the relatives, from 14 to 70 years of age, of gouty patients. In fact, hyperuricemia may be the only sign of the disease throughout the life of the individual. Of the more recent observers, Hill (22) found a positive family history of gout in 45 per cent and of fibrositis in an additional 15 per cent, and suggests that it may be a transmitted allergic state. In Cohen's (20) cases heredity appeared to play no role but the difficulty of obtaining a satisfactory family history in the patients of a large municipal hospital is evident. On the basis of this strong presumptive evidence, it must be assumed that the potentialities of the disease are present at birth, remaining dormant until some provocative factor invokes clinical activity. There appears to be a large sex-linked inheritance in gout with frequent transmission of the disease to the male through an unaffected female.

#### GOUT IN INFANCY

It is stated in Osler's Medicine (25) that "attacks of gout have occurred in infants at the breast" but no references to recorded cases are given. This statement has appeared repeatedly in the literature on gout for over 60 years and must be attributed to Gairdner (26) as no other author has made a similar claim. In his work "On Gout" published in 1860, he states. "That which will,

perhaps, be received with doubt is the fact which I have distinctly witnessed more than once, of a fit of painful gout in infants at the breast. I think I saw one child so affected, destroyed by pain alone." He quotes observations by Morgagni (27) to the same effect, the ancestral trait being the essential factor in all instances.

Of undoubted validity is the remarkable case of a  $3\frac{1}{2}$  week old breast-fed infant with proven gout reported by von Schopf (28) in 1930.

The infant was the third child of healthy parents, both of whose families were free from an ancestral or familial history of gout. Since birth, vomiting, which was at times projectile, occurred after each feeding. In the third week, severe restlessness appeared and the mother noted firm irregular lumps on the dorsa of both hands. These masses apparently involved the joints and marked contractures ensued. The lumps grew with extraordinary rapidity under observation and soon involved the wrists, elbows and ankles. The child died of bronchopneumonia on the 6th hospital day without any elevation of temperature. The postmortem examination disclosed diffuse sodium urate tophi in almost all the joints with extensive infiltrations of an identical nature in the kidneys, muscles, ligaments and many viscera. The kidneys in particular were studded with numberless white tophaceous masses. von Schopf emphasizes that all the usual causes of gout could be excluded and that the enormous amounts of uric acid contained in the tophi could only have arisen from endogenous purines, as there was no possible exogenous source.

#### GOUT IN CHILDHOOD

In 1823 Scudamore (29) stressed the exemption of youth as a feature of gout and suggested that the commonly asserted cases of gout in children were really examples of rheumatism. He nevertheless cited a group in which the age incidence of the first attack was as follows: at the age of 8, one; 12, one; 15, one; 16, one; 17, one; 18, four; 19, three. He admitted that most of these figures were obtained from patients and hence not entirely trustworthy; he had personally witnessed very few instances of gout before the age of 20. In 1876 Garrod (19) emphasized youth's relative immunity from the disease and also questioned the accuracy of the age incidence of Scudamore's cases. He in turn described 4 examples of what he deemed proven instances of juvenile gout, all with strong hereditary predisposition. The first was a boy of 17 with recurrent podagra who had his first attack at 16; the second was a girl of 10 with classical episodic podagra since the age of 7; the third was a boy of 12, whose first attack of podagra occurred at 9; the fourth a girl of 8 with recurrent ankle involvement. In the more recent literature Still (30) describes the case of a girl of 12 who had her first attack of gout at the age of  $3\frac{1}{2}$  with involvement of an ankle; there were recurrences every few months with pain, swelling and dusky redness of the metatarsophalangeal joint of the great toe. The temperature did not exceed  $100^{\circ}\text{F}$ . The attacks invariably subsided within 48 hours after the administration of Vinum Colchici. There is a strong ancestral history of gout in this instance, her father having suffered with frequent episodes of podagra since youth. Claiborne (31) cites the case of a 17 year old girl with a 3 year history of recurrent attacks of pain and swelling in the knee joint, usually provoked by minor injuries. The serum uric acid content was 7.5 mg. per cent. The exhibition of colchicine regularly brought prompt relief and was followed by a fall of the uric acid to normal levels.

## GOUT AND BLOOD DYSCRASIAS

The hyperuricemia usually accompanying a number of conditions such as leukemia, hemolytic anemia and polycythemia does not, as a rule, produce gout. There are, however, several recorded instances where gout appeared to supervene as a complication of a blood dyscrasia, chiefly leukemia or polycythemia. There is strong evidence that under both normal and pathological conditions the destruction of nuclear material in the bone marrow during the maturation of erythrocytes is an important source of endogenous uric acid. Glückman (32) has stressed the rarity of gout in leukemia and Magnus-Levy (33) also points out that the high uric acid content in the blood and the increased urinary output of uric acid fails to induce gout. Lambie (34) divides the instances in which gout and leukemia are associated into 2 classes (a) those with gout antecedent to the blood dyscrasia and (b) those in which the blood dyscrasia precedes the appearance of gout. The literature fails to disclose any instance of a child in the first class, but there have been several who fall into the second.

Vining and Thomson (35) report the case of a boy of 5 who had suffered for seven months from severe anemia, glandular enlargement and symmetrical multiple arthritis. In the last 2 months of life numerous tophi of the ears and olecranon processes appeared. At postmortem extensive gouty deposits in the joints and subcutaneous tissues were found and microscopic examination of the organs disclosed extensive leukemic infiltrations of the liver and kidneys. There was a strong hereditary incidence of gout in the families of both parents. Lambie (34) in a comprehensive review of gout and blood dyscrasias in childhood describes the case of a 14 year old boy with chronic erythronoclastic anemia of obscure origin, hyperuricemia, and diffuse gouty infiltrations with multiple tophi. Following splenectomy the tophi gradually disappeared with a fall in the serum uric acid level and improvement in the anemia. Roberts and Rose Bradford (36) had seen only one example in which gout and myelogenous leukemia were associated, in an old man with long standing gout. This despite the huge production of uric acid in the former disease. Glückman (32) collected 8 cases of leukemia associated with gout, but none were in children. Lambie (34) refers to a case of gout in a polycythemic boy of 18. Hench (37) points out that a gouty patient with coincident polycythemia or leukemia, is particularly prone to marked activity of his gout. Opsahl (38) cites 2 instances of podagra complicating blood regeneration, the first in a case of pernicious anemia treated with liver extract, the second following severe bleeding from a peptic ulcer. The patients had been on a purine free diet but the constitutional predisposition to gout was present. He believes that the purely endogenous uric acid produced by the disintegration of cell nuclei initiated the gouty arthritis.

## GOUT IN THE TEENS

Gout is by no means rare in the second decade, especially in the latter half. Reference to Table 1 discloses that approximately 2 per cent of sufferers from gout date their initial symptoms from this period. The onset of gout in the

teens, especially if unrecognized and inadequately controlled, is usually characterized by an accelerated tempo with crippling pain and invalidism within a few years of onset. On the other hand the disease is occasionally indistinguishable from the clinical picture of later years. Before the age of 20, tophi are rare (12) hyperuricemia is not pronounced (34) with occasional normal uric acid levels despite clinical severity (12), roentgen changes are infrequent (11) and vascular and renal complications are exceptional (22).

TABLE 1

*Age of patients at time of initial attack of gout from Br  chner-Mortensen (3) with additions*

AGE AT ONSET	SCUDAMORE (29) 1816	STRAND- GAARD (50) 1899	FUT- CHER (49) 1915	WIL- LIAMSON (5) 1920	COHEN (20) 1936	BR��CH- NER- MOR- TENSEN (3) 1940	MCCRACKEN ET AL (6) 1946	PERCENT- AGE INCIDENCE
0-10	1	0	0	0	0	0	0	0.09
11-20	12	7	1	0	4	2	1	2.42
21-30	142	18	5	17	12	4	13	19.19
31-40	194	40	17	43	23	25	21	32.90
41-50	118	35	28	34	17	26	30	26.16
51-60	38	10	25	21	6	24	28	13.75
61-70	10	11	13	1	1	16	more than 61 7	5.13
71-80	0	0	3	0	0	1		0.36
Total.....	515	121	92	116	63	98	100	100.00

## CLINICAL FEATURES

The clinical features of gout in early life may differ in some respects from those observed in adults. Tophaceous deposits which make their appearance in more than 50 per cent of adult sufferers from gout are only exceptionally encountered in youth. This is explained by the repeated observations (1, 5 and 10) that an average interval of from 15 to 20 years has been found to elapse between the initial symptoms of the disorder and the appearance of tophi. In the rare instances of "fulminating gout" in infancy and childhood which are often associated with blood dyscrasias, multiple and at times huge tophi have been described (28 and 35).

Although podagra is the most frequent single gouty manifestation in youth, polyarticular involvement, especially early in the disease, is more commonly observed than in adults (19 and 39). Whereas podagra appears at some stage of the disease in more than 90 per cent of adults (14) its total absence is more

common in youth (3). The tempo of juvenile gout also tends to be more rapid and more difficult to control, in this manner resembling juvenile diabetes. Onset at an early age often presages severe and frequently recurring seizures not infrequently leading in later years to severe crippling as well as renal and vascular injury. It has been repeatedly observed (21 and 36) that the younger the individual the more likely are the attacks to be polyarticular and migratory in character.

Obesity is infrequently seen in juvenile gout, thus differing sharply from its preponderance in adults (5 and 10). In fact, the so-called "constitution of gout" which some observers have described (40) is rarely detected in youth. Although some degree of renal impairment has been repeatedly observed in a large proportion of older sufferers from gout (41) this complication is rare in early life. Similarly, the vascular vulnerability identified with this disease in later life is exceptional in young persons.

#### CASE REPORTS

*Case 1. History.* S. L. (Adm. #501015) a 46 year old native born Jewish salesman was admitted to The Mount Sinai Hospital, on the Medical Service of Dr. George Baehr, on February 20, 1943 with advanced disabling gout and congestive heart failure.

At the age of 14 he had a sudden nocturnal attack of excruciating pain in the proximal joint of the right great toe which was red, swollen and exquisitely tender for a week thereafter. His weight was then 240 pounds. There were recurrences of an almost identical nature 3 or 4 times a year throughout his teens which were limited to the same toe. After the age of 20, the left great toe, ankles, wrists and elbows were affected. After 35 there was progressive deformity and stiffness of the severely involved articulations, particularly the hands. At about this time diabetes mellitus appeared and was easily controlled with diet and occasional small supplements of insulin. At 38 he had an episode of right renal colic with hematuria. This was soon followed by a brief bout of fever and oliguria. Following cystoscopy a uric acid stone was passed. Multiple joint involvement of unprecedented severity appeared after this manipulation and he was compelled to remain in bed for 9 months. Despite the disability associated with the recurrent gouty seizures and the increasing articular deformities he managed fairly well until the appearance of dyspnea and anginal pain a year prior to admission. He had several attacks of nocturnal paroxysmal dyspnea with progressive orthopnea and edema of the legs in the following months. Three weeks before he entered the hospital the distal end of the left 5th toe was amputated because of an infection.

The diagnosis of gout was not made until his late twenties. A familial or hereditary history of the disease could not be obtained.

*Examination.* The patient was overweight, plethoric and moderately dyspneic. There were numerous tophi on the helix of each ear. The heart was enlarged, the rhythm regular and loud musical systolic murmurs were heard over the entire precordium. There were congestive rales over both lower pulmonary lobes and a small effusion in the right pleural space. The brachial and radial arteries were sclerosed and tortuous. The blood pressure was 154 systolic, 92 diastolic. The liver descended as far as the umbilicus and there was some ascites. There was massive edema of both legs.

The joints were widely affected by gouty arthritis. The metacarpophalangeal joint of the index finger of each hand and the proximal interphalangeal joints of the 3rd, 4th and 5th fingers bilaterally were markedly deformed. The right elbow and ankle were badly distorted and motion was restricted. There were large irregular tophi on both olecranon processes.

*Laboratory data.* Hemoglobin was 77 per cent. The leucocytes numbered 9,050 with a



normal differential. The blood chemical figures were: urea 12, glucose 210, cholesterol 300, and uric acid 15.9 mg. per cent. The uric acid level later fell to 7.5 of which 95 per cent, or 7.14 mg. was bound. The pleural fluid uric acid was 6.8 mg. The blood Wassermann was negative. The urine showed a persistent trace of albumin with occasional granular casts and rare erythrocytes; glucose and acetone were absent. The electrocardiographic pattern was that of severe myocardial disease.

X-rays of the skull showed a small sella turcica, calcification of the internal carotid arteries and petro-clinoid ligaments and a small calcified pineal body. The right hand disclosed marked deformity of several of the interphalangeal joints with characteristic radiolucent punched-out circular zones such as are seen in gout.

*Course.* The congestive failure was rapidly controlled with digitalis, ammonium chloride and mercupurin with the loss of 15 pounds in a few days. In view of the hyperuricemia dehydration was carried out cautiously lest an attack of acute gout be precipitated. It was felt that in the presence of advanced gout and diffuse arteriosclerosis, without hypertension or a history of rheumatic infection, severe coronary artery sclerosis was the most probable interpretation of the vascular picture. It was also deemed likely that the musical murmurs were the result of calcification of the aortic and mitral valves.

This is an example of the severe form of advanced tophaceous gout appearing as a late sequel of juvenile podagra. It must be presumed that the long standing hyperuricemia contributed both to the renal calculous disease and to the general and coronary arteriosclerosis. The extreme obesity described at the time of the initial symptoms at the age of 14, has been rarely observed in juvenile podagra.

*Case 2.* B. B., a Jewish male residing in New Brunswick, Canada, was stricken with his first attack of classical podagra in October 1941, when he was 16 years of age. He had left school at 15 to work in his father's livestock business, which was largely devoted to the preparation and sale of cattle and hogs. He also, on occasion, assisted his older brothers in their meat and grocery store. A strong liking for meat, combined with its low cost and accessibility, led to a consumption of from 3 to 4 pounds a day by each male member of the family. During the hunting season, liberal quantities of venison and game supplemented this intake.

In the spring of 1941 he began to peddle meat to the neighboring farm community, disposing daily of a large "side of beef" on a 25 mile route. It was his custom to lunch on at least 2 pounds of his stock, usually cooked by a friendly farmwife. He was able to do justice to an additional pound or so of meat at his evening meal. His work exposed him to all types of weather, with considerable dampness and frequent rains. Aside from occasional mild colds and infrequent sore throats, his health had been excellent. He smoked 4 cigarettes a day, and drank beer in moderation. Whenever the opportunity arose, he engaged actively in athletics.

He was the youngest of 5 children ranging in age from 16 to 30. His parents and siblings were in good health. Painsstaking efforts to elicit a familial or ancestral history of gout were unavailing. The patient's father had an attack of "rheumatism" involving a knee joint 25 years previously which incapacitated him for 3 months; there was no recurrence. Attempts to obtain blood uric acid levels from the other members of the family were unsuccessful.

He was awakened early one morning in October 1941 by severe pain in the right great toe which was promptly intensified on attempting to walk. Within a few hours, the area became dusky red, swollen and the mesial surface of the toe was exquisitely tender. On the 2nd day the swelling extended to include most of the dorsum of the foot. Large doses of aspirin were required to control the pain. The highest temperature was 100.5°F. On the 4th day the pain and swelling began to subside, and by the 7th day there were no symptomatic residues. He had no further discomfort until 4 months later when without any

prolimina, or preceding respiratory infection, he experienced an almost identical episode with involvement of the same metatarsophalangeal joint. Subsequent recurrences appeared at 2 or 3 month intervals, and although they varied in severity, were usually incapacitating. He was totally asymptomatic during the intervals between seizures, and was able to resume work without difficulty. On 2 occasions the involvement, of lesser degree, was confined to the left great toe. In January 1944, again without preliminary infection, he developed a severe polyarthritis affecting chiefly the knees, elbows and finger joints. Curiously enough aside from ephemeral pains in the feet, the metatarsophalangeal articulations were not involved in this attack. A diagnosis of rheumatic fever was made and he was kept in bed for the next 6 months, despite the subsidence of the articular pain and swelling after a few weeks. The patient states that a persistently accelerated sedimentation rate and the fear of cardiac disease were the basis for the prolonged bedrest. He further avers that there was no anemia or other abnormality in the blood count, no cardiac disturbance was ever detected and the electrocardiogram was repeatedly negative. He resumed limited activity in August 1944, and aside from intermittent mild diffuse arthralgias, invariably unrelated to barometric changes, was not uncomfortable. Physical exercise, however, had been severely curtailed. In January 1945 he attended his sister's wedding where he danced energetically much of the night and consumed liberal quantities of a variety of alcoholic beverages. He awakened the following morning with an extremely painful and disabling polyarthritis; most of the peripheral joints were affected with painful swelling of both great toes. The crippling was so severe that he was bedfast for 5 months. After a period of slow improvement, he was able to assume minor tasks for about 2 months, when in August of that year he experienced another attack, this time of unprecedented duration and severity, which persisted with scarcely any remission until he visited New York in June 1946. The disease, although intense, was again limited to peripheral joints, the ankles, knees, fingers, wrists and elbows, with recurring swelling and tenderness. Despite the extent and severity of the disorder, the temperature rarely rose above 100°F. and the pulse was reported to be uniformly slow.

When referred for examination on June 11, 1946, he was in obvious distress and could scarcely walk because of pain. Notwithstanding his prolonged invalidism his color was ruddy. His weight was 154 lbs.; height 69½ inches. The tonsils had been removed, the teeth appeared normal and there was no suggestion of paranasal disease. Tophi were neither seen nor felt and there were no palpable lymph nodes. The right knee and ankle, the left wrist and elbow were slightly swollen and moderately tender. There was distinct "spindling" of the 3rd and 4th fingers of both hands. The pulse rate was 68, temperature 99.2°F, respirations 18 and the blood pressure 126 systolic, 78 diastolic. The heart was not enlarged, the sounds were of good quality and no murmurs were audible. The peripheral arteries were soft and the retinal vessels normal. The neurological survey was entirely negative. On fluoroscopic examination, the pulmonary fields were clear, and the cardiac configuration normal in all planes. The electrocardiogram was negative.

X-rays of the knees, feet, ankles, elbows and fingers failed to show any abnormality. Repeated urinalyses were negative. The serum uric acid was 6.8 mg. per cent. The sedimentation rate was moderately accelerated, 22 mm. in 1 hour (Westergren). The hemoglobin was 16.4 gm., the red blood cells 5.4 million. The white blood cells numbered 6,800 with a normal differential.

On the basis of the episodic involvement of the great toes with completely free intervals in the early stages of the illness as well as the hyperuricemia, it was felt that the patient had gout. He was accordingly given colchicine gr. ¼ at three hour intervals for three days and four times daily thereafter. A relatively low purine-low fat regime was also instituted. Aside from slight diarrhea on the 3rd day, which necessitated omitting several doses of the medication, he tolerated the regime without difficulty. Within less than 24 hours after colchicine was instituted, he showed distinct improvement, and at the end of three days was completely relieved of all articular pain. The edema about the larger joints disappeared although the deformity of the fingers persisted. He volunteered the opinion that

he had not felt as well in more than 2 years. On the 6th day of therapy the colchicine was further reduced to 3 tablets a day. The serum uric acid level had fallen to 4.6 mg. per cent and the sedimentation rate to 14 mm. in one hour. At the end of 2 weeks he danced for several hours with no ill effects. He soon resumed full athletic activities, including distance and competitive swimming. He was then placed on a maintenance dose of colchicine, three tablets daily for three days each week.

This patient remained in comparatively good health until December 1946 when he complained of weakness, nausea and intermittent vomiting and manifested progressive pallor. There was marked albuminuria and the blood urea nitrogen was 142 mg. per cent. The cause of the uremia was obscure. He was admitted to the Mount Sinai Hospital on January 21, 1947 under the care of Dr. I. Snapper. Blood chemical studies confirmed the presence of uremia with the urea nitrogen level always exceeding 140 mg. per cent; the uric acid was 7.4 and the creatinine 4.5 mg. per cent; the  $\text{CO}_2$  combining power was 37 volumes per cent. The urine contained 2 per cent albumin and the specific gravity was fixed at 1.010. The hemoglobin was 51 per cent, red blood cells 2.8 million and the differential count was normal. The renal failure was explained, in measure, by the discovery, on retrograde pyelography, of congenitally small kidneys with a rudimentary pelvis and absent calyces on the left. In view of the possible nephrotoxic effect of colchicine, the drug had been withheld. Within a few days, the joint manifestations which had been in almost complete abeyance for several months returned with great severity; both great toes became swollen and intensely painful. Liberal quantities of salicylates and neo-cinchophen were totally ineffective in relieving the distress. When colchicine was resumed after a 12 day period of uninterrupted joint pain, relief was immediate. It was felt that the gouty diathesis was probably accelerated by the renal insufficiency and consequent hyperuricemia. The patient was discharged from the hospital on February 13, and died at his home two weeks later. An autopsy was not obtained.

This case is described in some detail to stress the probable influence of a large purine diet, fatigue and repeated exposure to adverse barometric conditions in precipitating gouty arthritis in a youth of 16. In the absence of such combination of provocatives, it is quite likely that the inherent gouty trait may well have remained latent until later life, or perhaps, never manifested clinical activity. The accelerated tempo, severe crippling and relatively early transition to a polyarticular pattern is more characteristic of gout in youth than in adults. The disappearance of podagra coincident with the advent of polyarthritis deserves mention as it is an occurrence not uncommon in early life. The patient was mistakenly treated for rheumatic fever and spent a total of 2 years in bed. The course was largely afebrile, at times subfebrile, and the sole positive findings were the recurrent arthritis and moderately accelerated sedimentation rate. The response to colchicine was dramatic with prompt subsidence and rapid disappearance of all signs and symptoms.

*Case 3.* This case is reported through the courtesy of Dr. Martin G. Vorhaus.

*History.* V. K., a 27 year old unmarried female clerk was admitted to the Hospital for Joint Diseases on February 2, 1938 complaining of a painful swelling of the right knee joint of 3 days duration.

At the age of 12 she suddenly experienced severe pain in the left great toe which soon became red, swollen and tender; there was moderate fever and distinct malaise, with complete remission at the end of a week. During the next few years many similar attacks, usually of shorter duration, involved the same toe. A diagnosis of "arthritis" was made and she was treated with salicylates and local applications. The attacks recurred several times a year but were more frequent in the fall. At the age of 16, in addition to inter-

mittent involvement of both great toes, she began to experience, at irregular intervals, attacks of pain in the ankles, knees, elbows, wrists, shoulders and hips. Swellings of variable size in the fingers, wrists and knees accompanied the episodes and disappeared completely within two weeks. The attacks would occur characteristically in the evening, last 2 or 3 days and gradually subside. Since the age of 20 the left great toe had gradually increased in size with the appearance of a large irregular painless mass. Pain and difficulty in walking occurred solely with acute exacerbations and aside from the distortion of the toe she was quite comfortable between episodes. The patient observed that for the past year or two there had been some residual swelling of the right knee, right wrist and left ring finger. Three days prior to admission the right knee had become acutely swollen, red and tender and there was some fever. She had never observed any relationship between the attacks and the ingestion of purines, the occurrence of menses or other factors, but did note that on several occasions the acute arthritic symptoms were preceded by an upper respiratory infection.

The patient had scarlet fever at the age of 9 which was followed by transient hematuria, pneumonia at 10 and malaria at 10½. The menses appeared at 12½, have been regular and relatively painless. A tonsillectomy was performed at 22. She smoked 10 cigarettes a day.

An ancestral or familial history of gout could not be elicited. The cause of the deaths of 3 grandparents was unknown and one grandparent, both parents and 4 siblings were in excellent health.

*Examination.* The patient was somewhat short and stout and had excessive hair on the upper lip and a tendency to a male escutcheon. The head was disproportionately large. There was slight bilateral prominence of the eyes and moderate lateral nystagmus. The fundi were negative and the pupillary reactions normal. A cystic node about 2.5 cm. in diameter was felt in the right lobe of the thyroid. The heart and lungs were normal. Blood pressure was 112 systolic, 70 diastolic. Abdominal and rectal examinations were negative.

There was a doughy irregular mass the size of a pear adjacent to, and apparently arising from, the first left metatarsophalangeal joint; in some areas it had a cystic quality. The overlying skin was violaceous but not tender. Over the right Achilles tendon there was a huge mass 25 cm. in circumference, of similar consistency, with some increased warmth and slight tenderness. Similar enlargements were present in the distal phalanx of the right 4th finger which appeared to consist of discrete pea-sized nodules. The second and fourth metacarpophalangeal articulations of the right hand were also irregularly enlarged.

*Laboratory data.* The diagnosis of gout with advanced tophaceous disease was established by the blood uric acid level of 13.5 mg. per cent. Subsequent levels ranged from 7.8 to 14.6 mg. The urine showed a persistent trace of albumin with occasional leukocytes and erythrocytes; the specific gravity varied from 1.008 to 1.012. The hemoglobin was 86 per cent and the red cells numbered 5.2 million. There was a persistent leukocytosis with counts ranging from 10 to 16,000. The differential count was normal. The sedimentation rate was 56 mm. on admission and remained high throughout the entire period of observation. Blood chemical figures were normal except for the elevated uric acid. X-ray studies of the involved skeletal areas were highly suggestive of gout with punched-out vacuolated areas at the head of the 3rd right metacarpal, the semilunar bone on the left and the scaphoid bone on the right. The bones of the feet disclosed a destructive process involving the distal one-third of the shaft of the first metatarsal bone on the left side associated with some fragmentation. Arthritic changes were present in the terminal interphalangeal articulation of the great toe on the right. Irregular punched-out areas with circumferential sclerotic changes were seen in the right ala of the sacrum bordering on the sacroiliac joint. X-rays of the kidneys disclosed almost complete casts of both pelves, indistinctly outlined. The skull showed a moderate increase in the vertical diameter of the sella without any erosion.

Aspiration of a small effusion in the tophus on the right heel produced a moderately viscid yellowish liquid in which numberless monourate crystals were found.



*Course.* The patient was treated according to the plan of Vorhaus and Kramer (8) with 2,000 units of vitamin B<sub>1</sub> daily. There was the usual immediate reaction, which was followed by some reduction in the size of the tophus of the left foot. A bout of severe pain during the course of treatment was promptly relieved with colchicine.

She was readmitted to the Hospital on September 9, 1939 for excision and debridement of a painful urate abscess of the left great toe. The excised material was described as consisting of a handful of cheesy substance which infiltrated between muscle bundles, fat and even tendons. On microscopic section the connective tissue and muscles were found to be widely impregnated with tophaceous urate deposits. The latter consisted in large part of aggregates of needle-like urate crystals which had provoked a foreign body giant cell reaction. The blood uric acid was 14.7 mg. per cent.

Three subsequent admissions between November 1940 and April 1941 were for the excision of painful tophi and drainage of gouty abscesses. When last seen in August 1941 she had a draining abscess between the great and second toes on the left and required crutches to get about.

This is a striking example of the rapid evolution of severe disabling tophaceous gout appearing in the twenties in a woman who had her initial attack of podagra at the age of 12. Whereas the earlier episodes had been characteristically monarticular and limited to the great toe, polyarthritides and multiple tophi appeared after the age of 20. The disease remained undiagnosed, and hence untreated, until her admission to the hospital at 27. By this time crippling was severe and the tophi had reached huge proportions. Hyperuricemia had become extreme, the x-rays revealed the classical circumscribed punched-out areas at the ends of the bones and the tophi were frequently infected and required drainage. Excised connective tissue and muscles disclosed wide impregnation with tophaceous urate deposits. Despite the irreversibility of the process and the inexorable course of the disease, colchicine regularly brought a measure of relief.

*Case 4.* This case is presented through the kindness of Dr. Kermit E. Osserman.

G. S. a 35 year old native born housewife and camp counsellor had her first episode of podagra at the age of 16. For the last 6 months, she has had almost constant pain in both index fingers and persistent painful enlargement of both great toes.

The patient's maternal aunt had a polyarthritides for many years and the serum acid level was found to be 6.5 mg. per cent. Her mother had intermittent pain in both feet in her thirties and polyarticular pain for the last 10 years; at a recent examination a well defined tophus was found on the 4th finger of the right hand and the serum uric acid level was 4.95 mg. Her maternal grandmother had "rheumatism" for much of her life.

The patient had always been vigorous, engaging actively in most sports. Aside from occasional attacks of otitis media, she had been in uniformly good health. She had not interrupted her work as an athletic counsellor at a summer camp.

At the age of 16, she had the first of a long series of acute explosive painful swellings of the right great toe. The attacks were invariably sudden in onset, would appear with no apparent cause, at any time, and the intense pain was limited to the right metatarsophalangeal joint; attempts to walk at the height of the seizure would induce excruciating pain. The episodes lasted from 4 hours to 2 or 3 days and subsided rapidly. There was no discomfort between attacks, the free intervals lasting as long as 3 or 4 months. Subsequently the left metatarsophalangeal joint became involved. There was no history of preceding respiratory infection, dietary indiscretion or trauma; there was no seasonal incidence. Her diet was in no way remarkable. The disturbance was repeatedly accredited to poorly fitting shoes and the true nature of the condition was not suspected.



In April 1946 pain appeared in the index fingers of both hands. This was soon followed by pain and tenderness in both wrists and increasingly painful and persistent swellings in both great toes. There has been no remission and she has had almost constant discomfort in the affected joints.

On examination her nutrition was normal. The distal phalangeal joints of both fingers were slightly tender but not swollen. Both wrists were tender. There were painful prominences about 1 cm. in diameter and which appeared tophaceous over the metatarsophalangeal articulations of both great toes and the mesial aspects were extremely tender. The heart was normal and the remainder of the examination completely negative.

X-rays of both hands disclosed an occasional minute interstitial tophus, indicating minimal gouty arthritis. There were several rarified, at times punched-out, areas in the distal phalanges of both hands. Large tophi were seen on the dorsal surface of both metatarsophalangeal joints of the great toes. It was felt that the x-ray findings in the feet and hands were characteristic of gouty arthritis.

A single serum uric acid reading was 4.0 mg. per cent. The erythrocyte sedimentation rate (Westergren) was 20 mm. in one hour. The hemoglobin was 86 per cent. The white and differential counts were normal.

This is the only instance in this group in which an hereditary history of gout could be elicited. The pattern of recurring episodic gouty arthritis limited to the great toe with the appearance of severe polyarthritis many years after the initial podagra, has been closely followed in this case. Although the serum uric acid was not elevated, the history, classical x-ray findings and tophi establish the diagnosis of gout.

#### DIAGNOSIS

The medical heritage of most physicians is to believe that gout, especially in young individuals, is almost non-existent. Once the possibility of gout is entertained, accurate diagnosis should not be difficult. The history of sudden acute recurring attacks with complete remissions, especially in the early stages of the disease, is a pattern particularly distinctive of gout. Although other forms of rheumatism, such as rheumatic fever and rheumatoid arthritis, may also manifest some degree of remission and recurrence, they tend to be more gradual in onset and do not have the explosive or rapidly crescendo quality of an attack of gouty arthritis. Episodes of rheumatic fever usually make their appearance 7 to 14 days after a sore throat or other streptococcal infection. Although attacks of gout may be provoked by dietary and alcoholic excesses, minor traumas, strenuous exercise, and exposure to damp and cold, the role of infection appears to be insignificant. Gout may be further differentiated from rheumatic fever by the relatively low temperature, absence of nosebleeds, sweats, electrocardiographic changes or cardiac involvement. There is a tendency to monarticular or, less frequently, peripheral joint involvement, nocturnal exacerbation, hyperuricemia and, as a rule, prompt relief with colchicine. The exquisite tenderness over the joint and the intensity of the pain also serve to differentiate gout from other forms of arthritis. An hereditary or familial history can often be elicited. The frequent affection of the peripheral and small joints in gout is in contrast to the rare involvement of the hip, shoulder and vertebral articulations. Hench (37) aptly refers to this distribution as the "gradient of articular vulnerability."

Gout may be differentiated from rheumatoid arthritis by the warmth and bluish-red appearance of the great toe or extremity rather than the cool, bluish-white and often clammy character of the joint in the latter disease. In podagra the maximum intensity of pain and tenderness is on the mesial aspect of the articulation rather than on the dorsum or plantar surface as in infectious arthritis. Except in the late and polyarticular stages of gout, remission with total disappearance of symptoms is the rule, a characteristic rarely found in infectious arthritis. The desquamation of the skin over a subsiding gouty articulation is to be contrasted with its absence in other forms of acute joint inflammation. Subcutaneous tophi should not be confused with the nodules of rheumatic fever or rheumatoid arthritis. Where the appearance of the tophi is not diagnostic, the nodule may be needled and the demonstration of sodium urate crystals or a positive murexide test will be conclusive (42). Gout may be distinguished from traumatic arthritis by the completely disproportionate reaction to even mild injuries and occasional exacerbation of the disease in a joint far removed from the injured area. A pyogenic joint may be differentiated from gout by the higher fever and constitutional symptoms. Although the appearance of a gouty joint may closely resemble that seen in pyogenic inflammation, the fever and constitutional symptoms are not as pronounced and the evolution is more rapid. Whereas gonorrheal arthritis is often monarticular, its tempo is slower, with less tenderness and redness of the affected joint.

#### PROVOCATIVE AND THERAPEUTIC TESTS

In the occasional instance where the clinical picture is atypical and the serum uric acid is not elevated, some observers have resorted to provocative tests (37). These consist in the administration of large quantities of purines or fats (48), alcohol, thiamin chloride or gynergen. The unpredictability of gout is such, however, that known instances will fail to respond to such a regime which will, either paradoxically or coincidentally, be followed by exacerbations of rheumatoid arthritis or rheumatic fever. Of much greater dependability is the therapeutic test with colchicine and a low purine diet. The specific and often dramatic improvement following the institution of these measures in the subjects of gouty arthritis serves as a simple and reliable diagnostic measure.

#### LABORATORY

Although hyperuricemia with levels exceeding 4 mg. per cent (Folin) is almost the rule in gout, occasional instances with normal uric acid concentrations, especially in children, have been recorded (37). In early life hyperuricemia is notably rare between attacks. There is generally no correlation between the intensity of symptoms and the serum uric acid fluctuations. Patients will at times disclose low uric acid figures at the height of a severe attack and conversely, high levels when asymptomatic.

Rapid sedimentation rates are found in the great majority of cases of acute gouty arthritis (2) and leucocytosis with an increase in neutrophils and a shift to the left is a common finding (42). It is curious that both these tests should be positive in a metabolic disorder in which there is no apparent infectious

element. In fact correction of all possible sources of infection did not restore the sedimentation rate to normal (42). A number of observers have failed to find any correlation between the serum uric acid levels and the sedimentation rate (2 and 3).

X-ray examination is of little value in childhood as the joints rarely show the circumscribed punched-out areas which are found in a large proportion of adult sufferers from gout (43).

#### TREATMENT

The metabolic defect in gout is an inherent trait and the gouty proclivity persists throughout life. There is thus no known cure for the disorder. Once it is established, however, treatment should be based on a recognition of the factors contributing to the deposition of sodium urate in the joints and tissues and leading to clinical activity. This is particularly applicable to the hereditary candidates for the disease, especially the children and siblings of gouty subjects. It is essential that these individuals avoid occupations which expose them to the dietary, emotional and traumatic provocatives of acute gouty arthritis. Excessive food indulgence and obesity are the two chief hazards.

The treatment of the acute attack, especially in early life, is on the whole satisfactory. Colchicine is the drug of choice and almost merits the designation of a specific. With a dosage of 1/100 or 1/120 grain every 2 or 3 hours the symptoms of even severe attacks are usually relieved within 36 to 48 hours. Various schemes for the administration of colchicine have been outlined, the majority recommending that the stated dosage be given at 1 to 3 hour intervals until diarrhea appears or the pain is under control. It also seems to have considerable value as a prophylactic between seizures and a maintenance dosage of 3 tablets daily for 3 consecutive days each week has repeatedly proven its effectiveness. The mechanism of the action of colchicine remains a mystery.

In occasional instances where intolerance or idiosyncrasy to colchicine exists, cinchophen, despite its occasional hepatotoxicity, is a valuable drug (37). It has also been used in conjunction with colchicine. When employed for any length of time, hepatic function should be carefully watched. Neocinchophen is much less toxic and often quite as effective. The supplementary exhibition of salicylates with either colchicine or cinchophen will at times hasten symptomatic relief and is usually well tolerated. Both cinchophen and the salicylates are effective in excreting variable quantities of uric acid (44).

Vorhaus and Kramer (8) have employed thiamin chloride in daily doses of 1 to 10 mg. and have secured moderate to marked relief in 12 of 25 gouty patients after 1 to 3 years of treatment. Therapy was continued despite the flare-up of symptoms that occurred in the first 2 to 4 days after thiamin was administered in over 90 per cent of the patients. The authors believe that further studies are necessary to evaluate the relationship between gout and thiamin.

Although a purine-free regimen has long been axiomatic in the management of gout, the bulk of recent evidence supports the belief that this restriction has no effect either in controlling or preventing attacks (45). Similarly, despite

the almost universally recommended total abstinence from alcohol, some observers have been unable to provoke attacks experimentally by the administration of large quantities of liquor (23). Notwithstanding this evidence, these authors agree that a reasonably low purine intake may have empiric advantages and recommend the elimination of sweetbreads, anchovies, sardines, liver, kidneys, brains and meat extracts. It would appear to be unreasonable, in view of the faulty excretion of uric acid in gout, to permit large quantities of purine containing foods. The diet should, however, be well balanced, containing adequate protein and vitamins. Fats should be restricted to prevent obesity. Some observers report distinct improvement on fat-low (46) others on fat-free (47) diets. Bauer and Klemperer (23) have been unable to secure any benefit from such restrictions.

#### SUMMARY

In view of the hereditary and constitutional nature of gout its relatively low incidence in early life has not been adequately explained. It is the generally accepted belief that the inherent trait is present at birth and in most cases remains quiescent until the 4th decade or later. The hyperuricemia that has been repeatedly observed in the symptomless kin of sufferers from gout should establish beyond cavil the familial and hereditary character of the disease.

Gout in infancy represents a profound metabolic error with urates derived chiefly from endogenous sources; the course may be fulminating. Its incidence in the early weeks and months of life is fortunately rare enough to be a curiosity. The disorder is sporadically observed in early childhood and is almost invariably limited to those with a strong hereditary taint. Gout is not uncommon in the second decade, especially the latter half and at least 2 per cent of the victims of the disease date their initial symptoms from this period. The traditional provocatives such as a high purine dietary, alcoholic excesses and obesity appear to play a lesser role in juvenile gout than in later life and the proportion of females is considerably higher.

As in most metabolic diseases that make their appearance in youth, the tempo of gout is much more rapid and disability more pronounced than when the initial symptoms appear in later life. This may be explained in part by the all too frequent failure to recognize the disease thus withholding palliative and preventive therapy. The repeated observation that an average of 10 years usually elapse between the initial symptoms and the correct diagnosis is particularly applicable to the juvenile form of the disease. Prompt recognition of the disorder at this age is exceptional.

Four cases of gout are reported in which the first attack of podagra occurred at the ages of 12, 14, 16 and 16 respectively. In one instance a huge purine dietary and repeated exposure to dampness and cold may have served as provocatives. In another there was extreme obesity. All presented advanced crippling gouty arthritis with, in 3 cases, extensive tophaceous deposits and severe deformity in later years. Renal impairment was evident in one, calculi in another. One case was complicated by severe general and coronary artery

sclerosis and probable calcification of the aortic and mitral valves. In no instance was the nature of the disorder recognized until the disability was advanced. In but one case could an hereditary history of gout be obtained.

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## HUARTE NAVARRO (JUAN DE DIOS), OF THE SIXTEENTH CENTURY

A FRIEND OF JEWISH PHYSICIANS

CAMILLE DREYFUS, M.D.

(*New York, N. Y.*)

The Renaissance, this brilliant era of the emancipation from the bondage of scholasticism, was an epoch of bitter hatred against the Jews in general, and the Jewish physicians in particular. In this era of enlightenment the papal bullae, those of Paul IV, Pius V, Gregory XIII, stated what their predecessors did in the XIIIth Century: "Preterea excommunicentur Christiani qui in infirmitate positi, causa medicine se committunt cure Judeorum" (1). "Furthermore, those Christians shall be excommunicated who, because of illness, entrust themselves for healing to the care of Jews." Martin Luther, although a heretic in the eyes of the Popes, was in full agreement with his former superiors in regard to Jewish physicians. In a Table Talk (April 11, 1539) he stated: "The Jews who pretend to be physicians rob their Christian patients of their lives and possessions with their drugs, for they believe that they serve God when they severely injure them and secretly bring about their death. We mad fools seek help from our enemies and thus tempt God" (2).

The fact that so many papal bullae and conciliar decrees had to be issued to prohibit medical care by a Jewish physician seems to prove that these Jewish physicians still were held in high esteem by public opinion. This was further shown by the fact that exceptions had to be officially granted: "Cum nullus alius medicus adest, vel cum est excellens aliquis medicus Judaeus" (3) "If no other physician is at hand or, if there is an excellent one among the Jews," then a Jewish physician may be consulted.

That this excuse was particularly good for high dignitaries is a well known historical fact. Nevertheless, Jewish physicians knew too well that rebellion against a papal decree could end at the stake. One of them warns his colleagues (4): "We Jewish physicians who live under the yoke of domination need special wisdom, because the Christian physicians envy us and form intrigues against us, and often we have to explain our scientific opinion and if they hear unknown things they say: 'He kills Christians.' Therefore, I advise that no Jew treat a Christian unless he is able to discuss natural science."

Jewish physicians also dared to take up the defense of Jewish practitioners. In one of his brilliant essays Harry Friedenwald (5) recalled some "Apologetic Works of Jewish Physicians." To be sure, it was a very courageous undertaking to file a protest against the official attitude of the Church. It amounted to open resistance and defiance of the ecclesiastical power.

David de Pomis of Spoleto (born 1525) was one of these dauntless defenders. His "De Medico Hebraeo Enarratio Apologica" gives evidence of the lofty religious, ethical and scholarly qualities of the writer, qualities the more ad-

mirable when we remember the condition of "captivity" under which he lived (Friedenwald).

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FIG. 1

"Jewish physicians have been dwelling among the Christians for 1,500 years," he wrote. "They have been regularly called to the sickbed of Christians; never yet has anyone been charged with a crime. On the contrary, they have dis-

tinguished themselves honorably among their professional colleagues. Nor is it remarkable that they exercise such care, pains and industry for they are strangers

#### Chap. XIV. The Trial of *Monsieur*

But the most powerful Argument in my Opinion to this Purpose, is, that when *Francis de Valois* King of *France* was seized with a very tedious Sickness, and that the Physicians of his House and Court could give him no Ease, he said every time the Fever returned, that it was not possible for any Christian Physician to Cure him, and that he expected from them no Relief. Inasmuch that one time being Impatient to find himself every day worse with his Fever, he ordered a Courier to be dispatch'd to *Spain*, to desire the Emperor *Charles* the Fifth, to send him a Jew Doctor, the best of all his Court, from whom he hoped to receive a Remedy for his Distemper, if there were any in the Art. There was no little Laughing in *Spain* at this Request, and all concluded that it was no other than the Conceit of a Man in a Fever. But for all this the Emperor was not wanting to give Order that such a Physician as was required, should be sought after, if he were to be found, though he were out of the Kingdom, and when none could be met withal, they sent him a Physician newly turned Christian, hoping thereby to comply with the King's Curiosity. But the Physician being arrived in *France*, and brought to the King's Presence, there past between them a most agreeable Dialogue, wherein was discover'd, that the Phy-

V 3

ician

and the captives of war and, therefore, subservient to the individual Christians. No one has ever witnessed any crime by a Jewish physician and no one has

received reliable information of such. It is only because of a common prejudice that we are accused and suffer injury. When Christians accept falsehood for

#### The Tryal of Wilts. Chap. XIV.

fician was a Christian, and therefore the King would take no Physic at his Hands. The King from the Opinion he had conceived of the Physician's being a *Jew*, asked him by way of passing the time, if he was not as yet weary of expecting the Messiah promised in the Law? The Physician answered, Sir, I expect not the Messiah promised in the Judaic-Law. You are the wiser for that replied the King, for the Signs set down in the Scripture to know his Coming are already accomplished a great while ago. The number of days (rejoined the Physician) we Christians keep well the Account of, for there are now a Thousand five hundred fourty and two Years determined since he came; he abode in the World Thirty three Years, at the end of which, he died on the Cross, and rose again the third Day, after which he ascended into Heaven, where he now Reigns. Why, saith the King, you are a Christian! Yes, Sir, by the Grace of God, answered the Physician. Then, said the King, be gone to your own Country in good time, for I have Christian Physicians enough in my own Court and House, I took you to be a Jew, who in my Opinion are those that have a Natural Ability for Cures. And so he took leave of him without allowing him to feel his Pulse, or examine his Urine, or mingle the least word concerning his Distemper. And forthwith sent to *Constantinople* for a Jew, who recovered him only with Asses-Milk.

truth they harm themselves more than us, for this is completely contrary to the teachings of Christ. Why have princes and prelates sought Jewish physicians?



Because of their crimes and wrongdoings or because of their ability and their good treatment?"

Almost at the same time a Spanish Gentile physician and philosopher, Huarte Navarro (Juan de Dios) published a treatise in which he endeavored to prove that the aptitudes to the different professions is dependent on the temperament of the individual nation. He discerns clearly that medicine depends on two things: First, a thorough methodical knowledge of the principles of medicine and, second, a great experience with patients. Jews, in his opinion, have these qualities.

Who is Huarte Navarro Juan de Dios? He was born in Saint Jean de Pied de Port in Navarra in 1529. He died at the end of the sixteenth century (1589). He studied at the University of Huesca where he graduated as a medical doctor and, after some years of travelling, practiced medicine there (6).

His treatise had an extraordinary success. Between the years of 1575-1652 there were not less than eight Spanish editions, six Latin, four Italian, six French and three English translations (De Irate counted 41 editions)—almost a kind of "non-fiction best seller."

The treatise was dedicated to Philip II, his Catholic majesty of Spain. The French translator was so enthusiastic about Huarte's book that he dedicated his translation to Louis XIV. "I would sin," he writes, "against the grandeur of this work and against the intention of the author if I presented it to anyone but a king." It is difficult to explain why a book so laudatory for the Jewish physicians, so contrary to the official statements, could escape the severe control of the censor.

It may be that François I's opinion in regard to Jewish physicians was too dangerous to be contradicted.

In 1632 a French physician, Jourdain Guibelet (7), *médecin du Roy* in Evreux, in a malicious pamphlet expressed his suspicion that Huarte may "well have some part of judaism in his soul" (*C'd'avoir en l'âme quelque pointe de judaïsme*). This suspicion is unfounded, else the Great Inquisition which was at its height at this time would have made an easy prey of the author.

But the importance of the book cannot be dismissed. At a time when official decrees considered Jewish physicians as criminals, when ecclesiastical authorities menaced with excommunication every Christian treated by a Jewish physician and when Jewish physicians risked the stake in defending themselves, a non-Jewish physician stated that Jews are (by birth) the best physicians.

At first glance the chapter on medicine is but one among others. But if we consider that the author is a physician, it could well be that he used all other considerations as a cover to mask his main purpose—to defend Jewish physicians.

Huarte's influence was still alive at the end of the 18th and in the 19th Century. Théophile de Borden (8), Cabanis (9) and, as late as 1855, I. M. Guardia (10), have given full account of Huarte's work and respectful praise for his original and dauntless ideas.

More recently de Irate commented on Huarte's work. His monograph (11), published in 1938 at Münster, Westphalia bears as a sub-title: "Contribution

to the History of Differential Psychology." This otherwise thorough study does not elaborate on our quotation, which is to be expected, being printed in Hitler Germany. Goebbels' censor, more than the Great Inquisitor, would not have tolerated any eulogistic remark on Jewish physicians. Perhaps the author did not need any censor.

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# PROTRACTED ILLNESS IN CHILDREN, A PROBABLE CAUSE OF HORMONAL DEFICIENCY. THE EFFECT OF THYROID THERAPY\*

GERTRUDE FELSHIN, M.D.

AND

ANNE TOPPER, M.D.

(New York, N. Y.)

A special Clinic for Growth and Development at the Mount Sinai Hospital provided opportunity to observe and treat children of stunted growth. In appraising disturbances of growth and development it is necessary to consider many factors such as racial and familial heritage, the influence of nutrition and environmental factors and the effect of disease. Of these only the third factor can be influenced by specific medical measures alone. It is reasonable to assume that any disease that interferes with normal nutrition and normal oxidative processes of the body may contribute to disturbances resulting in endocrinopathies. In some cases the endocrine disturbance may be so mild as to escape detection while in others it may be so severe as to contribute to irreversible structural changes. For example, malnutrition may lead to gonadal dysfunction (1), and many children with diabetes, although tall at the onset of the disease, may become substantially stunted (2).

In this paper we have selected children whose growth disturbances appeared to be the result of disease with possible coincident involvement of the endocrine glands. Stunted growth was found to be most frequently associated with such conditions as congenital heart disease, allergy, chronic infection and intestinal parasitic infestation. The large number of patients studied fall into the foregoing four groups, each of which is illustrated by a case history.

1. *Congenital heart disease* is foremost in retarding growth and development (3). The technique of angiocardiology and the excellent clinical results obtained by tying off a patent ductus arteriosus, make it now possible to obviate the further developmental retardation that occurs in this type of lesion. Other types of congenital heart disease may be more difficult to treat.

In such cases as the following summary illustrates thyroid therapy has a beneficial effect.

*Case 1. History.* P. M., a boy 5 years of age, was observed as a case of interauricular septal defect since birth at a Board of Health Clinic. Examination showed a child, well compensated, and not cyanotic, whose outstanding characteristic was stunting of growth. In January 1942, he weighed 31 pounds and was 36½ inches tall. (The normal range for this age is 41 to 45 inches.)<sup>1</sup> X-ray of his carpal centers showed marked retardation of bone growth (fig. 1a).

\* From the Pediatric Service of Dr. Murray H. Bass.

<sup>1</sup> Figures of normal height range are taken from graphs established by the Department of Pediatrics, State University of Iowa.

In October 1944, the boy was referred to the Growth and Development Clinic. He was then  $7\frac{1}{2}$  years of age. His height was 38 inches (an increase of  $1\frac{1}{2}$  inches during the previous two and one-half years). X-ray of the carpal centers again showed marked retardation with very little progress since the previous film (fig. 1b). His basal metabolism was within low normal limits. Because of the marked stunting in growth and retardation of bone growth the child was given thyroid therapy. Bearing in mind that in patients with cardiac disease thyroidectomy is sometimes performed in order to maintain a low metabolism it seemed desirable to keep the thyroid dosage small in order not to increase the boy's basal metabolic rate unduly. The child received  $\frac{1}{4}$  of a grain daily, which was gradually increased to 1 grain. There were periods during which the thyroid extract was omitted entirely, especially during the summer months.

On this regime, the boy has been observed by us at infrequent intervals for two years. (The mother was not completely cooperative because of the birth of two children during this time.) He is now 11 years of age. He weighs 55 pounds and is  $46\frac{1}{2}$  inches tall. His basal metabolic rate is still within normal limits. An x-ray of the carpal centers taken in November 1946 showed a bone growth fairly consistent with his chronologic age (fig. 1c).



FIG. 1. a. Case 1. P. M. Chronologic age five years—bone age, at most three years.  
 b. Case 1. P. M. Age, seven and one-half years. Note: There has been very little progress in bone growth.  
 c. Case 1. P. M. Age, nine and one-half years, two years after thyroid therapy. Note: Bone growth greatly accelerated, but still retarded.

*Comment.* In this case, it would seem that thyroid therapy afforded stimulation to growth, as during two years of observation without thyroid therapy the boy grew  $1\frac{1}{2}$  inches and there was very little progress in bone growth. During the two years of thyroid therapy, the child grew  $8\frac{1}{2}$  inches and bone growth was markedly accelerated. The child is still undersized. The cardiac condition which caused the disturbance in development is still present. It is apparent, however, that the thyroid hormone served as an extra stimulus to growth which a poorly nourished gland was evidently unable to maintain. The dosage was small and inconstant. Perhaps a larger dose and more continuous administration of the hormone would have given better results.

II. *Allergic children* constitute the second group treated in the Growth and Development Clinic. All the manifestations of allergy (infantile and childhood eczema, diarrhea and vomiting, hayfever and asthma) are seen in childhood. Frequent attacks of asthma may interfere with rest, appetite and nutrition. When the history of a child referred to the Clinic gives reason to suspect the existence of allergy the patient is sent to the Allergy Clinic for investigation.

If an allergy is found treatment is simultaneously instituted for both the allergy and the endocrinopathy. This is essential since the allergic condition is frequently chronic as is the endocrine condition. Were the endocrine disturbance to remain untreated until the allergy is controlled irreversible damage might result. Furthermore, the response of the allergic condition to treatment is frequently better when endocrine imbalance is corrected.

The following case illustrates the effect of such combined treatment on the development of an allergic child.

*Case 2. History.* S. J. was first seen in January 1940 at the age of 2½ years. She weighed 35½ pounds and was 36 inches tall. She was apparently well except for a generalized eczema which had persisted for six weeks. The child was given an ointment for temporary relief and was asked to return for study within a short interval. She was lost sight of for three years when she appeared in the Allergy Clinic in June 1943. She was now 6 years old. She weighed 40 pounds and was 43 inches tall. She had a severe generalized eczema with many impetiginous areas. The scalp was involved and the sparse hairs matted together. The skin condition was too severe to allow immediate cutaneous testing. Schick and Mantoux tests were negative. The blood examination was normal except for a hemoglobin of 65

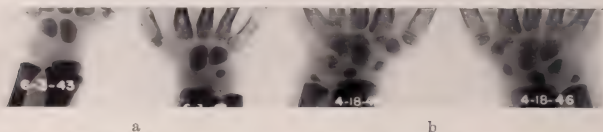


FIG. 2. a. Case 2. S. J. Chronologic age, six years. Bone age, from two to three years.  
b. Case 2. S. J. Chronologic age, eight years and ten months, two years and ten months after thyroid therapy. Note: Bone growth greatly accelerated.

per cent. The child was dull and apathetic. Roentgenograms of the wrists showed a four year retardation in bone age (fig. 2a). Thyroid (desiccated U.S.P.), ½ grain daily, was advised and later increased to 1 grain, then to 1½ grains. The child was put on an elimination diet, irritating elements in her environment were removed, and a skin ointment was given. Within a month the skin was sufficiently clear to permit skin testing. The child was found sensitive to a great number of foods, dust, feathers and pollens. Desensitization to dust and pollens was instituted. The child's condition improved considerably. Her hemoglobin rose slowly to 81 per cent and she began to gain weight and to grow. She became mentally more alert. Her skin and hair gradually resumed a more natural texture. In April 1946, after less than three years of therapy, the child had grown 10 inches and had gained 35 pounds. An x-ray of the wrists taken at this time showed bone growth to be within the normal limits for her age (8 years and 10 months) (fig. 2b).

*Comment.* This child was not stunted in growth, she was 43 inches tall. The normal range in height for this age is 42½ to 46 inches. However, the marked retardation in bone growth suggested a possible hypofunction of the thyroid gland, and thyroid therapy was tried. After three years of combined desensitization and thyroid therapy, the child grew 10 inches. She was now in the tall zone of height range instead of the low zone. (The range for this age is from 47½ inches to 53 inches.) In this case, the thyroid therapy apparently stimulated the child's growth to its greatest potentialities.



III. *Intestinal parasitism* is commonly seen in this clinic. This is readily explained by the fact that the population in the immediate vicinity of The Mount Sinai Hospital is largely Puerto Rican. Ortiz (4), who has had a wide experience with tropical diseases, has often stated that almost all children coming from Puerto Rico have intestinal parasites. Practically all these children are stunted in growth. The following case illustrates the satisfactory results that can be obtained by treating not only the parasitism, but also the stunted growth.

*Case 3. History.* J. R. was admitted to our Clinic in June 1945, at the age of 9 years. The physical examination showed an underdeveloped, undernourished Puerto Rican boy with generalized adenopathy and a palpable spleen. His hemoglobin was 65 per cent, and he had an eosinophilia of 12 per cent. Heterophile reaction was negative. His basal metabolic rate was 993 calories per twenty-four hours ( $\pm\%$ ), a low normal. His Was-



FIG. 3. a. Case 3. J. R. Chronologic age, nine years. Bone age, about six years.  
b. Case 3. J. R. Age ten years, one year after thyroid therapy. Note: Bone growth within normal limits.

sermann and Mantoux tests gave negative results. Stool examination showed the presence of *Trichiuris* (whipworm). The child weighed 43 pounds and was 44 inches tall. (The normal range is from 50 to 53 inches.) Roentgenogram of the wrist showed marked retardation in bone growth (fig. 3a).

Because of the marked stunting in growth and bone development, the child was given 2 grains of thyroid daily. He was given an adequate diet fortified by vitamins and iron, and thyroid therapy was continued. He was not treated for the *Trichiuris* until November 1946. By June 1946, one year later, the child had grown 4 inches and had gained  $6\frac{1}{2}$  pounds. An x-ray of the carpal centers showed a normal bone age at this time (fig. 3b). The basal metabolism was normal.

*Comment.* In evaluating the improvement shown in this case we must take many factors into account. The boy was born of Puerto Rican parents, who themselves are of short stature. The boy had lived in Puerto Rico for the first eight and one-half years of his life. The native diet on this island is known to be inadequate. His stunted growth therefore was the result not only of his disease but of his heritage and environment. The child's lowered metabolism and the delay in bone growth pointed to a possible disturbance of the endocrine

glands concerned with growth, and thyroid extract may to some extent correct this.

IV. *Chronic and persistent drains on the body by recurrent upper respiratory infections* in early childhood add to the problems of disturbed growth.

The following case is that of a child who was subject to an almost uninterrupted series of infections.

*Case 4. History.* J. B. was first seen in our general Pediatric Clinic in 1938 at the age of 5 years. At that time he was already stunted in growth. He weighed  $33\frac{1}{2}$  pounds and was 38 inches tall. (The normal range is from 42 to 45 inches.) His tuberculin test was positive. He gave a history of repeated upper respiratory infections, several attacks of tonsillitis and otitis media followed by tonsillectomy and mastoidectomy, all before the age of 5.



FIG. 4. a. Case 4. J. B. Chronologic age, eleven years. Bone age, from eight to nine years.

b. Case 4. J. B. Age, twelve and one-half years, after one and one-half years of thyroid therapy. Bone growth within normal limits.

For the succeeding six years the boy was observed at intervals at the Pediatric Clinic. He was given an adequate diet and vitamin intake, with an occasional sojourn at a Preventorium and a Convalescent home. During these six years infections were minimal and the child did well. He gained 22 pounds and grew 10 inches. However, he remained stunted in growth. In June 1944, at the age of 11, the child was referred to the Growth and Development Clinic. He weighed 55 pounds and was 48 inches tall. (The normal range is from 54 to 59 inches.) The physical examination was essentially negative. The blood examination was normal. The basal metabolic rate was 1,112 calories per twenty-four hours, which is within the normal limits. The boy's mental development was definitely retarded and he was several grades behind in his school standing. An x-ray of the wrists showed a severe retardation in bone growth (fig. 4a).

The child was given  $1\frac{1}{2}$  grains of thyroid a day, which was later increased to 2 grains, in addition to an adequate diet and vitamin intake. After one and one-half years of this treatment, the child showed an increase of  $6\frac{1}{2}$  inches in height and had gained  $21\frac{1}{2}$  pounds in weight. An x-ray of the wrists at this time was within normal limits (fig. 4b).

*Comment.* This case presents further evidence of the effectiveness of thyroid extract on growth. During the six years of observation without thyroid therapy, the growth increment was 8 inches. During the succeeding one and one-half

years, while receiving thyroid extract, the increment was  $6\frac{1}{2}$  inches. The acceleration in bone growth was also notable. The basal metabolism remained within normal limits. His general status has improved considerably, and there was very satisfactory improvement in school standing.

Of course, the natural acceleration of the growth impulse in early puberty cannot be entirely ignored, and during the period of thyroid therapy this child was in early puberty. However, it has been established that thyroxin is a metabolic catalyst that speeds the metabolism in the direction in which it is going (6) and if, as in this case, the thyroid therapy speeded up metabolism in the direction of growth, its use was justified.

#### DISCUSSION

In reporting these four cases, each representing a large group, we have emphasized the importance of trying to stimulate retarded growth in children whose lack of development seems to be secondary to the presence of disease which lead to endocrine dysfunction. In these cases the endocrine dysfunction did not appear to be the original basis for the disorder present. The growth stimulating properties of the thyroid hormone are well known (7). Its effect on morphology is best seen in young animals. This is most clearly shown by the retardation and cessation of growth in thyroidecomized animals. Gudernatsch (8), Allen (9), Morse (10), Uhlenhuth (11), Swingle (12) and many others were able to accelerate the growth and development of animals by feeding them thyroid extract.

The dramatic effects of the hormone in congenital myxedema are too well known to need comment. That the growth stimulation afforded by the hormone is not limited to the cretin has been stressed, among many others by Topper, and Topper and Cohen (5).

The thyroid gland plays a very important role in the development of the osseous system (14). In juvenile hypothyroidism, there is a delay in the appearance of bone nuclei, as well as in epiphyseal union. Clinically, the number of centers of ossification of the carpal bones is widely used as a basis for determining the skeletal development. Although there is great variation in the time of their appearance, usual delay frequently indicates a lack of thyroid secretion.

Thyroid is not the only growth stimulating hormone in the body. The anterior pituitary gland elaborates a hormone which Hammett calls the "intensity factor of growth" (15). Evans and his co-workers (16) have presented evidence for the existence of such a hormone. The effect of this hormone is best seen in experimental animals. Hypophysectomized animals fail to grow and develop. The hormone will restore growth in these animals. However, at the present time, the evidence for the effectiveness of the growth hormone in human beings is still far from convincing (17). In fact, some authors stress the fact that "No one has demonstrated growth in man without the concomitant use of thyroid extract, which (in their opinion) is responsible for any success obtained" (18).

In recent years, much was published in support of the concept that growth is accelerated through androgenic stimulation. The androgenic hormone also has an influence on bone growth. Normally for a period of time, the production of

androgens hastens skeletal development without ossification of the epiphyseal cartilages. Later, androgen is produced in greater amounts, leading to closure of the epiphyses and cessation of growth. These changes occur normally in the pubescent boy, and probably similar changes can be induced by administering the hormone in the underdeveloped boy (19). There are, however, certain undesirable and possibly harmful consequences attendant upon its use, which have been listed by Aub and Katy (20) as follows:

1. Suppression of the male reproductive function through pituitary inhibition.
2. Possible premature epiphyseal closure in adolescents in whom stimulation of growth is being sought.
3. Masculinizing effects in females, some of which, such as hirsutism and voice changes, seem to be permanent.

Wilkins and Fleischman (21) experimented with nine different androgenic steroids on dwarfed children, but failed to find a related steroid which would be of practical value on growth stimulation and still be free from the undesirable virilizing effects.

These studies indicate that in spite of the growth stimulation afforded by this androgen, its use in childhood is not yet justified.

It is difficult to obtain dependable criteria for the effectiveness on growth of any endocrine therapy. Therapy that is still questionable, as in the case of the pituitary hormone, as well as the androgenic hormone should be avoided. The thyroid hormone, which has a proven effect upon growth, is simple to administer and can be easily controlled.

#### SUMMARY

Four groups of ailing children in whom growth was stunted are reported. Each group is illustrated by one case.

It is probable that in these cases the stunted growth and retardation of bone development indicated that the endocrine glands were affected adversely by disease, disclosed by thorough physical and laboratory investigations. The disease and the endocrine disturbance were treated simultaneously.

The effect of thyroid therapy in promoting growth in these children was noted in their increased height and acceleration of bone growth during the period of treatment and led to the conclusion that such therapy is an effective, safe and simple method of stimulating growth.

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## A CASE OF WATERHOUSE-FRIEDRICHSEN SYNDROME DUE TO HEMOPHILUS INFLUENZAE

GEORGE J. GINANDES, M.D. AND JORGE E. HOWARD, M.D.

(New York, N. Y.)

*From the Pediatric Service of the Mount Sinai Hospital*

Since the syndrome of fulminating purpura associated with adrenal hemorrhage has been accepted as a clinical entity (1), the literature has been much enhanced by case reports and comprehensive reviews (2). The dramatic character of the disease and its sudden tragic termination have given considerable impetus to the discussion of pathogenesis and pathology, as well as to the search for all possible etiologic agents.

With regard to pathology, there is little or no reason for confusion. The adrenals have been described as the site of more or less extensive hemorrhage. The most common lesion is a hemorrhage which is medullary in origin, and extends by diffusion into the cortex. The glands may, however, show numerous focal hemorrhages. Occasionally thrombosis of the suprarenal vein has been reported; but its rarity suggests the likelihood that this is secondary to the adrenal hemorrhage. Occasionally only one adrenal is involved.

The adrenal hemorrhage may be sufficiently massive at times to rupture through the capsule into the peritoneal cavity. This type is more common in the newborn period (3), and has been related to the trauma, asphyxia, and venous congestion associated with birth. The purpuric skin lesions, which may be extensive, are thought to be either the result of a widespread toxic destruction of the capillaries and arterioles, or of multiple bacterial emboli. Although congestion of the vessels of the leptomeninges is found, meningitis of the frank purulent variety has only rarely been described. This fact is probably related to the rapid course of the disease. The other organs of the body, including the liver and spleen, show the pathologic findings usually associated with sepsis.

The pathogenesis of the Waterhouse-Friedrichsen syndrome is not completely clear. The disease is predominantly a disease of childhood. Lindsay and his associates noted that 90 per cent of the patients are under 9 years of age (4). The sequence of events is usually sepsis, adrenal hemorrhage, adrenal failure, circulatory collapse.

The laboratory findings show a retention of non-protein nitrogen and creatinine. A hypoglycemia is generally present. There is usually a moderate leucocytosis which may, however, be quite marked. The blood chloride levels have been reported normal. Sodium and potassium levels have been studied in isolated cases. In two cases reported by d'Agati and Marangoni (5) there were no striking changes. In one case there was slight sodium retention with a low potassium; in the other, the sodium and potassium were approximately normal. Jacobi and Harris (6) and Sharkey (7) cite single cases in which the

sodium was low. The finding of a relatively normal serum sodium, potassium and chloride levels is not surprising in view of the work of Loeb, Atchley *et al* (8) who observed that even when total adrenalectomy was performed in animals, the daily rate of reduction of sodium was as little as 2.3 mg. per liter.

The lack of correlation between the degree of adrenal hemorrhage and the severity of clinical symptoms has always been puzzling. Although fairly extensive hemorrhage of the adrenals is commonly seen, it is frequently difficult to explain the clinical symptoms on the basis of demonstrable adrenal pathology. This fact has caused many to question the role of the adrenal in the syndrome. Menenghello in Chile (9), Williams in Australia (10), and London and Holman (11) in this country, reported cases which, while clinically fulfilling the criteria of the syndrome, failed to show evidence of adrenal hemorrhage at necropsy. Gordon and Shimkin (12) described a typical case in an adult, in which the striking finding was focal areas of necrosis in the pituitary, with only minimal adrenal findings.

Jacobi and Harris (6) make the observation that even though significant adrenal hemorrhage may not be seen, there is present considerable cortical cellular necrobiosis to explain the pathologic physiology.

Some observers, including Thomas and Leiphart (13), maintain that even when adrenal hemorrhage and secondary adrenal insufficiency are present, it does not offer a tenable explanation of death in the syndrome. Experimentally this view finds support in the work of Swingle (14) with bilaterally adrenalectomized dogs, in which the symptoms of adrenal insufficiency did not appear for several days after operation. This lag by far exceeds that which occurs in the ordinary fulminating case in humans.

In the light of the clinical and experimental data available, it must be accepted that severe sepsis can produce a picture which is clinically and chemically indistinguishable from the true Waterhouse-Friedrichsen syndrome, and in which final differentiation can be made only at necropsy.

The relationship of the Waterhouse-Friedrichsen syndrome to the thymico-lymphatic status has been emphasized by numerous authors (15) who consider this of significance in pathogenesis. Bamatter (16) thought that the hypoplasia of the adrenals shown to be associated with the thymico-lymphatic state predisposes to adrenal apoplexy. Sofer (17) analyzed the records of five cases at the Mount Sinai Hospital. All the patients were children. Two of the five showed considerable thymic enlargement with a visceral lymphadenopathy. A third child, 1½ years of age, showed marked hyperplasia of Peyer's Patches. Kunstadter (2) and Herbut and Manges (18) question the relationship between the thymico-lymphatic state and the Waterhouse-Friedrichsen syndrome and present considerable clinical and pathologic evidence to support their contention.

The search for the bacterial etiology of the Waterhouse-Friedrichsen syndrome has been hampered by the rapid course of the disease, which frequently makes accurate laboratory studies impossible. Martland (19) as late as 1944, expressed the view that all cases are due to massive invasion with meningococci. He

supports this view by pointing to the seasonal incidence of the disease, and to the pathologic findings, which he considers characteristic of meningococcal infection. Other authors, while emphasizing the predominant etiologic role of the meningococcus, also point to the streptococcus (20), staphylococcus and pneumococcus (21) as etiologic agents. Lindsay and his associates (4) in 1941 reported two cases in which hemophilus influenzae B was isolated, and one case *Neisseria Flavus* Type 2 was found. Many other organisms have been implicated, but the evidence frequently leaves doubt as to their etiologic relationship.

The question of the etiologic agent is no longer of sheer academic interest. The availability of penicillin, streptomycin, the sulfonamides, and the appropriate antitoxic and antibacterial sera, makes possible a selective approach to the management of the sepsis. This along with satisfactory replacement and supportive therapy for the adrenal and circulatory failure, should reduce the mortality.

The following case of Waterhouse-Friedrichsen syndrome died within two hours after admission to the hospital. It is reported because certain unusual features were present. The course prior to the onset of serious symptoms was prolonged. The spinal fluid was frankly purulent, and the organism isolated from it as well as from the blood was hemophilus influenza B.

#### CASE REPORT

*History.* (Adm. #541498.) B. S., a boy, 4 years of age, was seen by us in the reception ward of the Mount Sinai Hospital on November 7, 1945. The history obtained from the parents was as follows: The child was well up to two days prior to admission. Towards evening of this day, he complained of a mild headache, and refused to eat. His temperature was found to be 103°F. He was restless during the night, and the symptoms continued until the afternoon of the following day, when he suddenly had a shaking chill. The headache became worse; the child appeared to be drowsy, and the temperature rose to 106°F. The family physician was urgently called, and he examined the child at this time. He found no satisfactory explanation for the high temperature. He prescribed aspirin, and returned that evening to re-examine the child. The temperature at that time had dropped to 102°F. The headache seemed somewhat improved, the child seemed comfortable and drank fluids eagerly. He spent a restful night, and when awakened on the morning of admission, he felt well, sat up in bed, and ate his breakfast. The temperature however remained elevated to 103°. At 10 a.m. he suddenly vomited, had two diarrheal stools, became cyanotic and drowsy. The temperature rose to 106°F.

The family physician saw the child about this time, and in view of the alarming temperature and the sudden change in the child's condition, he recommended hospitalization. *En route* to the hospital, the child was well oriented, spoke easily, and the cyanosis, though generalized, was slight.

*Examination.* The child was seen by us in the admitting room at 12 o'clock noon. He was obviously in shock and comatose. His entire skin was cyanotic, cold and clammy, and presented a diffusely mottled appearance. The cyanosis and mottling was more marked over the lower extremities and was intense enough to resemble post mortem lividity. Petechiae were not found on the skin or mucous membranes. The rectal temperature was 106.4°F. The peripheral pulse could not be felt. The heart sounds were very faint and distant. There was a tachycardia with a rate of 200, and an embryocardia. He was markedly tachypneic. The respiratory rate was 80 per minute. Supra and infraclavicular retraction were present.

The lungs were normal to percussion and occasional rales could be heard at the right base. The abdomen was distended. The liver edge was felt about 5 cm. below the costal margin. The spleen was not palpable. Except for slight nuchal rigidity and the obvious comatose state, the neurologic examination was negative. The blood pressure could not be measured.

The history and the physical examination suggested a Waterhouse-Friedrichsen syndrome. Accordingly, the following treatment was promptly instituted in the reception ward. The patient was placed in an oxygen tent in shock position. Through a continuous intravenous drip, 150 cc. of a 2 per cent solution of sulfadiazine was given. This was followed by 250 cc. of plasma, and thereafter a continuous drip of normal saline. Adrenal cortical extract was administered, the child receiving a total of 20 U intravenously and 10 U intramuscularly within an hour; 100,000 of penicillin were given intramuscularly. With this treatment, he seemed to improve somewhat. The blood pressure rose to a systolic of 30 mm. The liver then rapidly enlarged, and the heart sounds became weaker. Despite stimulation and the use of digifoline, the child died in the reception ward approximately two hours after admission, and 48 hours after the onset of his earliest symptoms.

*Laboratory data.* The laboratory findings, necessarily curtailed because of the precarious condition of the child, revealed the following: The blood count showed 12,000 white blood cells with a normal differential count. The hemoglobin was 85 per cent. The electrocardiogram showed a sinus tachycardia, rate 230, with right axis deviation. There was a depressed RST segment in leads 1, 2, and 4, suggesting coronary insufficiency. The blood culture yielded a profuse growth of hemophilus influenza B. The spinal tap, deferred because of the patient's condition, but performed within a few minutes after exitus showed cloudy fluid, which on smear and culture revealed hemophilus influenza B. The fluid contained a total protein of 165 mg. per cent, sugar 35 mg. per cent, and a normal chloride content of 667 mg. per cent.

*Necropsy findings.* Autopsy revealed multiple petechiae diffusely distributed in the pericardium, the subendocardium and subpleural tissues, the peritoneal and retro-peritoneal tissues, as well as in the lungs. The heart showed a somewhat flabby and moderately dilated right ventricle, with a firm left ventricle. In the epicardium there were a large number of focal hemorrhages, ranging in size from pin point to 3 cm. in diameter. The lungs showed evidence of pulmonary edema and severe congestion. The liver was enlarged and congested and weighed 825 Gm. The spleen was enlarged and weighed 100 Gm. A small accessory spleen was present. The thymus was apparently normal and weighed 28 Gm. There was generalized lymphoid hyperplasia.

Both adrenal glands presented on their posterior surfaces areas of hemorrhage 1 to 2 cm. in diameter. The remainder of the adrenals showed the cortex well preserved, although there was marked congestion throughout.

Permission for brain and spinal cord study was not obtained.

#### COMMENT

The unusual etiology of the case presented deserves emphasis. The marked predominance of the meningococcus in cases of the Waterhouse-Friedrichsen syndrome causes one to lose sight of other possible bacterial agents. The clinical picture may give no clue to the etiology. In post mortem studies, analogous bilateral adrenal hemorrhages may be found.

The spinal fluid findings in our case are unusual in this disease. Generally the fluid is described as clear, and only infrequently can the organism be grown out on culture. In our case, the fluid was purulent, and the organism was easily found on smear as well as on culture. The total protein of the spinal fluid was 165 mg. per cent and the sugar content was reduced. These differences may of course be related to the nature of the organism, as well as to the duration of the

disease. The meningococcal infection generally has a fulminating clinical course. Death frequently occurs in a matter of hours. The influenzal organism is apparently apt to give a more insidious onset, and thus allow sufficient time to elapse for the meningeal reaction to be evident, before adrenal apoplexy occurs. This was apparent in our case as well as in the two influenzal cases in the Lindsay series. In Lindsay's cases too, the spinal fluid cell count was elevated, and the brain showed apparent exudate on its surface, in contrast to his meningococcal cases.

The appreciation of the broad scope of bacterial agents that may produce the disease is important, since the precarious condition of the patient frequently makes procedures necessary for complete bacteriologic workup hazardous. In the absence of an accurate etiologic diagnosis through petechial puncture (22) or culture, therapy must be all-encompassing. The inclusion of the influenzal organism among the proven causative agents makes it necessary to use streptomycin (23) in addition to penicillin and sulfadiazine, at least until the etiology is definitely established. Thereafter, the use of the most selective antibiotic along with the use of type specific antisera is of course justified.

Along with adequate antibacterial and antitoxic therapy, the need for adequate replacement and supportive therapy in the management of the circulatory collapse is pressing. This is particularly true since it is clinically impossible to distinguish those cases which have irreversible pathology from those in which shock is associated with only slight adrenal hemorrhage. The use of cortin intravenously and subcutaneously in large doses, and the judicious use of desoxycorticosterone intramuscularly is indicated. The treatment of the shock phase by adrenalin, oxygen, and intravenous infusions of plasma, glucose in saline, and blood, must be prompt and adequate.

With this combination of antibacterial replacement and supportive treatment, at least 22 recoveries have been reported in the literature since Carey reported his case in 1940 (24). Only two of these recoveries have been children. Weinberg and McGavack (25) summarized eleven of these cases from the literature and added one of their own. The other ten have been reported subsequently (26). All these 22 cases were due to the meningococcus except one case reported by Rucks and Hobson (27) in a child of 3, where the organism was staphylococcus aureus. It is possible that with the addition of streptomycin and appropriate sera, cases due to the influenzal organism may be successfully treated.

#### SUMMARY

A case of Waterhouse-Friedrichsen syndrome has been presented with necropsy findings. The etiologic agent was an unusual one—hemophilus influenza B. The course was somewhat prolonged. Lumbar puncture revealed a frankly purulent spinal fluid from which organisms were obtained on smear and culture. The variations in adrenal pathology seen in this disease are commented on. Because of the unusual organism that may be encountered, the use of all-encompassing regime of anti-bacterial therapy including penicillin, sulfadiazine and streptomycin, and appropriate type specific antisera is urged. Along with



this, replacement therapy for the adrenal insufficiency, and management of the circular collapse are vital.

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## EARLY CARCINOMA OF THE CERVIX; ITS PATHOLOGICAL AND CLINICAL ASPECTS

MORRIS A. GOLDBERGER, M.D. AND NATHAN MINTZ, M.D.

(New York, N. Y.)

*From the Gynecological Service of the Mount Sinai Hospital*

The classical and well advanced cases of carcinoma of the cervix usually present no diagnostic problem. The gross appearance is sufficient to arouse suspicion as to the true character of the growth, which is usually confirmed by microscopic examination of the biopsy specimen. The present treatment of carcinoma of the cervix, as judged by the end results, leaves much to be desired; and it is generally agreed that if the diagnosis could be made earlier, the number of cures would be markedly increased. Our present knowledge of the early changes in malignancy is still insufficient for absolute criteria concerning the degree of epithelial change necessary to fully justify a diagnosis of carcinoma.

Robert Meyer's (1) requirements for the histological diagnosis of carcinoma are atypical architectural pattern, anaplasia of the cells, and invasiveness. In considering the first requirement, he emphasizes that the cells of normal squamous epithelium present a characteristic tile-like arrangement in three distinct strata. In carcinoma, this normal stratification is lost by virtue of the rapid multiplication of the cells, and the epithelium is more compact because of the increased cellularity. His second requirement stresses the great disparity in the size and ripeness of the cells. In addition, the nuclei show lack of uniformity as to size, shape and staining qualities. Some nuclei take practically no stain and will show a prominent chromatin network; while others will be hyperchromatic. The nuclei show typical or atypical mitoses in lesser or greater numbers. The cellular borders may not be very clear and the cells lie in closely packed confusion. The third postulate, invasiveness, is evident when the epithelial growth has broken through the basement membrane and there is then no longer any question as to the malignant nature of the specimen. Robert Meyer is of the opinion that the diagnosis of carcinoma can be made without invasiveness. He believes that there is no single microscopic characteristic which justifies a diagnosis of carcinoma; and that in the final decision one must also include the clinical evaluation.

As early as 1910, I. C. Rubin (2) stated that the most important criterion of malignancy is the intrinsic morphology of the cells and that invasiveness and inflammatory change are not essential to the diagnosis. It is not at all unsound from a pathogenetic viewpoint, to postulate that these cells may have assumed the characteristics of malignancy without having as yet invaded the deeper tissue. It is naturally of the utmost importance for serial sections to be examined before one can say with any degree of certainty that there is no break through the basement membrane. The concept of carcinoma *in situ* or intra-epithelial

carcinoma is based on this premise, and it is a view that is championed by Schiller (3), Graves (4), Smith and Pemberton (5), and Broders (6).

In contrast to this view, Novak (7) and Martzloff (8) believe that as long as there is no invasion, there is no malignancy. Martzloff speaks of "non-invasive carcinomatoid change." Stevenson and Scipades (9) use the term "non-invasive, potential carcinoma of the cervix." The difference of opinion as to the minimal criteria which constitute malignant changes, prompted the report of the following two cases.

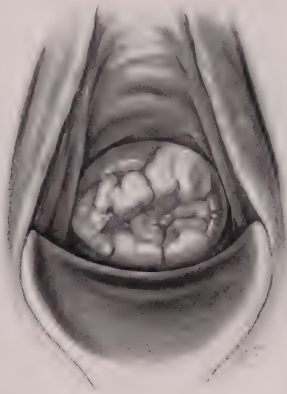


FIG. 1

#### CASE REPORTS

*Case 1. History.* (Adm. #546392) The patient, a white married woman, aged 35 years, gravida III, para I, had had two induced abortions in 1931 and 1932 respectively, and a full term pregnancy in 1934. In 1936 she contracted gonorrhea and since then had been unable to conceive. In January 1946, during the course of an examination by her local physician, a lesion was noted on the cervix. Her menses had been perfectly normal and there had never been any intermenstrual bleeding, vaginal discharge or any complaints referable to the reproductive tract. Although no diagnosis was established, several medications were tried, including penicillin both locally and systemically, without any regression, and after two months of treatment the patient was admitted to the Mount Sinai Hospital.

*Examination.* Positive findings were disclosed on pelvic examination only. It revealed an uninflamed parous introitus with normal external genitalia and vagina. The cervix was conical in outline and felt somewhat roughened in the vicinity of the external os. Circumscribing the external os was a circular area about one-half inch in diameter which was slightly raised above the surrounding tissue, closely resembling sugar frosting in appearance; this was sharply demarcated from the remainder of the cervix (fig. 1). There was no

discharge or bleeding from the cervical canal. The body of the uterus was unenlarged, anterior, firm and movable. The right adnexa were palpable but not unduly tender or cystic. The left adnexa felt normal. There was no infiltration of the parametria or *cul-de-sac*. Rectal examination was negative.

*Laboratory data.* The Wassermann, urine, blood count and cystoscopy were normal.

*Operative course.* A small portion of the whitish area was detached from the underlying cervix without difficulty and without producing any bleeding. The biopsy report (Surg. #90645) was: "Cervical mucosa showing leukoplakia with marked cell irregularity and mitoses highly suggestive of early squamous cell carcinoma (only epithelial layer present)."

An adequate wedge of cervical tissue was excised five days later and this (Surg. #90683) was reported: "Cervical tissue showing leukoplakia with one area of early carcinomatous change as seen in previous biopsy. No infiltration of cervical stroma" (figs. 2, 3 and 4).

A high cervical amputation was performed on March 28, 1946 and the pathology report on this specimen was as follows: "The specimen is an amputated cervix bearing 2.2 cm. of

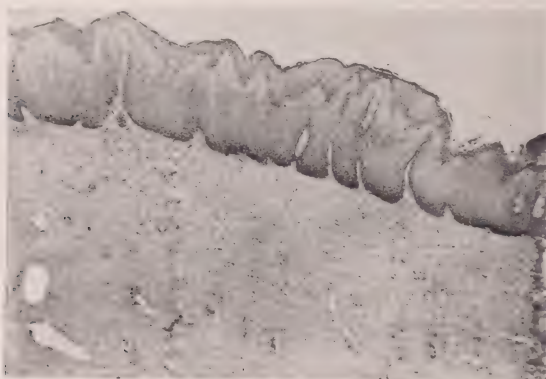


FIG. 2. Low power view of leukoplakia of the cervix showing areas of keratosis, hypertrophy and prominence of the papillae.

vaginal mucosa outside the external os and 3.5 cm. of cervical mucosa within the canal. At the external os there are two irregular acute ulcerations, measuring 5 and 10 cm. each. About the remainder of the circumference of the cervix there are seen irregular areas of granular, white epithelium extending 1.7 cm. into the cervical canal" (Surg. #90758).

Microscopically, there was an abrupt transition between the normal and abnormal mucosa. The leukoplakic area showed a thickening of the epithelium with keratinization of the outer layer. The papillae were more pronounced and dipped rather deeply into the connective tissue. The basal cells showed varying degrees of anaplasia, consisting of irregularity of cells and nuclei, hyperchromatism of the nuclei, loss of polarity of the cells, and an occasional mitotic figure. There was no break through the basement membrane by the abnormal cells.

The diagnosis was: "Cervix showing striking leukoplakia and proliferation of atypical squamous epithelium highly suggestive of early carcinoma *in situ*."

The postoperative course was uneventful and at the time of discharge (April 5, 1946), the cervix had healed completely. The patient was seen in the Follow-up Clinic June 14, 1946, when the findings were: "Cervix feels regular and is covered with normal epithelium."

*Case 2. History.* (Adm. # 553792) The patient, a white married woman, aged 47 years, gravida III, para II, first came to the Gynecology Out-patient Department of the Mount Sinai Hospital in October 1938 because of menorrhagia of several months' duration. A small fibromyoma of the uterus was diagnosed but operative treatment was deferred because



FIG. 3. Medium power view of leukoplakia of the cervix showing the considerable keratosis of the superficial layers.

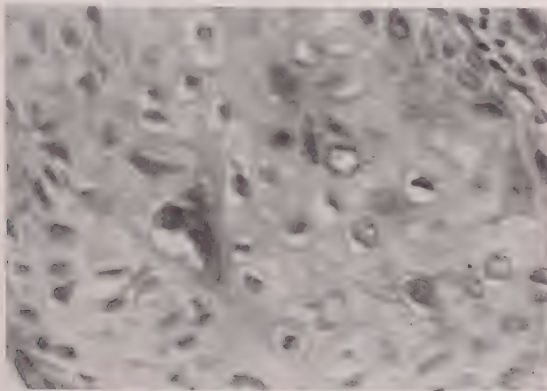


FIG. 4. High power view of the leukoplakia of the cervix showing area of cellular atypism, hyperchromatism, and mitotic figures.

the symptoms were minimal. At the time a note was made that the cervix was lacerated, eroded and bled easily, and 10 per cent silver nitrate was administered topically. The patient was seen on eight occasions during the next two years, and finally, because the menorrhagia was more pronounced and the tumor had grown in size, she was admitted to the Mount Sinai Hospital in June 1940.



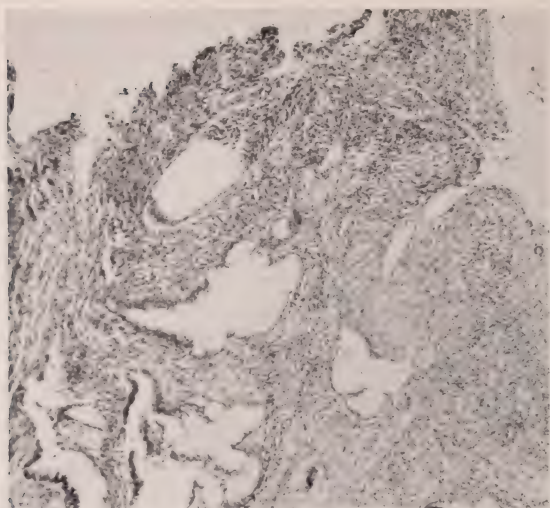


FIG. 5. Low power view of cervical biopsy showing chronic cervicitis and metaplastic squamous epithelium located at the mouths of two of the cervical glands.

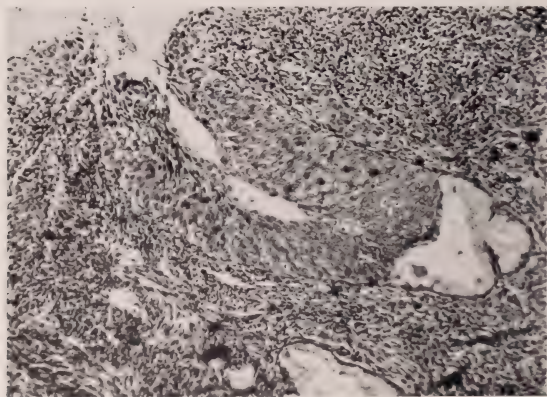


FIG. 6. Medium power view of one of the cervical glands showing the squamous cell metaplasia without evidence of invasiveness.

*Examination and course.* The general physical examination was essentially negative. The pelvic status showed a relaxed vulva and vagina. The cervix was lacerated and slightly eroded. The uterus was enlarged by a globular pedunculated tumor about 5 cm. in diameter. The right adnexa could not be differentiated from the mass. The left adnexa were easily palpable. The hemoglobin was 78 per cent; the urine and Wassermann examinations were negative. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed and the pathological report (Surg. #71111) was: "Fibroid uterus; bilateral chronic salpingitis; small parovarian cyst." The postoperative course was uneventful.

The patient was referred to the Out-patient Department of the Hospital for treatment of her menopause symptoms and between September 5th and November 7th, 1940, she received 7 mg. of estradiol dipropionate intramuscularly. In October of 1940 a biopsy was performed

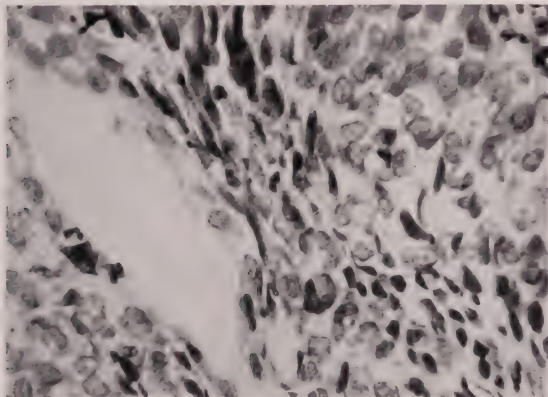


FIG. 7. High power view of this gland showing definite atypism, mitoses, hyperchromatism and giant cells.

for an erosion of the cervix, although the patient had no symptoms of pain, bleeding or discharge. The biopsy report (Surg. #72758) was: "Small fragment of cervical tissue showing chronic inflammation and areas of striking epithelial proliferation with many mitoses, suggestive of early squamous cell carcinoma. No definite diagnosis can be made" (figs. 5, 6 and 7).

The patient failed to report for the next ten months and in September 1941 returned because of recurrence of the menopausal syndrome. Between September 1942 and July 1946 she received estrogen injections sporadically by her private physician. In August 1946 the patient re-appeared at the Out-patient Department because she had noticed spontaneous vaginal bleeding on two occasions unassociated with any other symptoms. A biopsy of the cervix (Surg. #92061) was made and reported as follows: "Fragments of very anaplastic immature cell carcinoma. The type of carcinoma cannot be determined" (fig. 8).

The patient was then re-admitted to the Gynecological Service of the Hospital on September 7, 1946. The pelvic examination at this time revealed a normal vulva and vagina. The cervix felt small and irregular. The cervix was lacerated bilaterally and there was a granular erosion present on the anterior lip. The cervix was freely movable and the para-

metria not involved. The diagnosis of Stage I Carcinoma was made. The patient then received a full course of radiotherapy.

#### DISCUSSION

The two cases described showed the presence of an early carcinoma. The difficulties encountered in the diagnosis may be attributed to the differences of opinion as to the histologic changes necessary for the diagnosis of malignancy.

The histological findings in biopsy specimens often do not fulfill the accepted classical criteria for the diagnosis of carcinoma. It is hoped by reviewing the pathological, clinical and follow-up findings in early carcinoma, a clearer

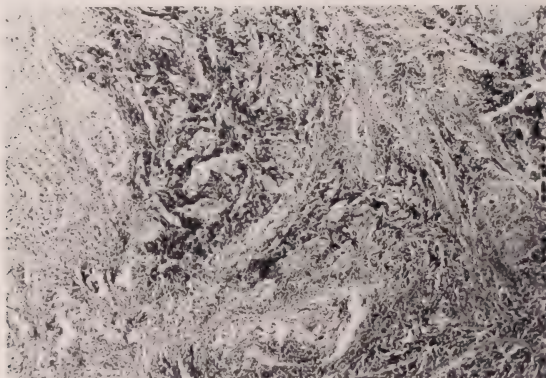


FIG. 8. Cervical biopsy of Case 2 six years after initial biopsy, showing anaplastic, immature type carcinoma with invasiveness.

conception may be obtained so that the diagnosis can be made before the occurrence of invasion into the surrounding tissues.

In our first case, leukoplakia of the cervix was found, the pathologist describing a proliferation of atypical squamous epithelium highly suggestive of early carcinoma *in situ*. The sections of amputated cervix did not show invasion at any point. Hinselman (10) describes four grades of histological changes in leukoplakia of the cervix: Grade or Rubric I, showing changes in the basal layer as a slight atypism of the cells. Grade or Rubric II shows in addition to marked hyperkeratosis, a thickened basal layer with considerable activity and mitoses of the cells. So far these changes cannot be accepted as criteria for malignancy, but the gap between Rubric II and Rubric III, as stressed by Novak, is significant in that the changes seen in Rubric III can be accepted as malignant, although as yet no invasion is seen. Rubric IV shows invasiveness. Although Hinselmann believes that Rubric I, II, III and IV show a gradual transition of pathogenesis and designates leukoplakia as a pre-cancerous

lesion, yet this conception is not satisfactory because of the gap between the benign and malignant stages.

We agree with most gynecological pathologists who object to the term "pre-cancerous lesions" because of the absence of adequate morphologic changes and its uncertain implications. Case I resembles that described by Hinselmann as Leukoplakia Rubric III. However, we would rather consider it as an intra-epithelial carcinoma arising in the basal layer of the cervix epithelium in the presence of hyperkeratosis of the superficial epithelial layers. We are fully aware that the lack of invasiveness in this case may be questioned as insufficient evidence for some to make the diagnosis of malignancy.

In Case II of our report, the first biopsy specimen did not show invasiveness, yet the intra-epithelial changes were significant enough and if encountered today, in view of our present conception, we would have considered the findings sufficient for a diagnosis of carcinoma, rather than suggestive of early carcinoma, as was reported. This patient returned six years later with a full blown invasive anaplastic carcinoma. It may be contended that this might be coincidental and independent of the presence of the original intra-epithelial lesion. In this case, the invasive character of the original intra-epithelial carcinoma developed in the course of time (six years). TeLinde and Galvin (11) quote cases in which eight and one-half years and three years respectively elapsed from the time when surface epithelial changes were first noticed and a diagnosis of invasive carcinoma was made.

The clinical importance of early carcinoma of the cervix must be stressed in view of this broadened concept of its histopathology. The invasiveness of malignant disease determines the method of its treatment. TeLinde and Galvin recommend total hysterectomy with removal of a vaginal cuff for the treatment of intra-epithelial carcinoma of the cervix. This gives them the opportunity to study the entire specimen and to make their final decision as to the correctness of their preoperative estimation of the cervix lesion. We feel that if the biopsy specimen shows an early intra-epithelial lesion, then amputation of the cervix will fulfill both of these objectives, as this procedure will remove the local disease and will also give enough material for serial histopathologic study to exclude invasion. In confining our treatment to amputation of the cervix, we have not deprived the patient of the benefit of adequate radium therapy by colpostat and intra-uterine tandem, in case the amputated specimen, after careful study, shows invasion. This is more adequate than total hysterectomy as we can not rely on postoperative x-ray treatment to eradicate possible parametrial spread. Total hysterectomy therefore is too radical in non-invasive intra-epithelial carcinoma of the cervix, and not radical enough, should invasion be found in the extirpated uterus.

The liberal employment of the biopsy of the cervix as a diagnostic aid in suspected cases is of paramount importance; but if the interpretation of the histological specimen is inconclusive, then amputation of the cervix is recommended, rather than repeated biopsies. Amputation of the cervix satisfies three conditions: 1. It removes the local lesion, 2. It supplies an ample specimen

for serial histopathologic study, 3. It does not interfere with the radical treatment by surgery or radiation, should invasiveness be encountered.

#### CONCLUSIONS

1. An attempt to diagnose early carcinoma is made on the histologic studies of intra-epithelial changes in the cervix.
2. Two cases of intra-epithelial carcinoma of the cervix are described.
3. Amputation of the cervix is recommended in suspected cases, rather than simple hysterectomy.
4. The method of treatment for non-invasive carcinoma of the cervix is discussed.

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## CHORIONEPITHELIOMA: HORMONAL STUDIES AND PATHOLOGICAL FINDINGS

EMANUEL KLEMPNER, M.D.

(New York, N. Y.)

*From the Gynecological Service and the Laboratories of the Mount Sinai Hospital, New York*

Chorionepithelioma presents a diagnostic and therapeutic challenge to the gynecologist. The laboratory investigator is fascinated, and still somewhat perplexed, by the biological activity of the tumor. Finally, the pathologist always finds it a fruitful field for careful study. The following case is reported because it presents interesting features from the clinical, biological, and pathological points of view.

*History.* R. G. (Adm. #545622) was a fifty year old, colored housewife, who had had a normal pregnancy and uncomplicated delivery at the age of twenty years. She had no serious illness or operation. Her menstrual periods began at the age of fourteen, occurred regularly every twenty-eight days, and lasted for four days. She had her last menstrual period on December 16, 1945. There was no bleeding in January, 1946, but on February 15, 1946, there was profuse vaginal bleeding, marked by passage of clots. She entered another hospital and there she passed some tissue. This, as was subsequently reported, was: "Placental tissue," diagnosed on pathological examination as hydatidiform mole. She refused surgical intervention and left that hospital against advice. She continued to bleed intermittently from February 15 until February 22, 1946, when she was admitted to the Gynecological Service of the Mount Sinai Hospital.

*Examination.* The patient was a well-developed woman in no distress. Temperature, 99.6°F; pulse rate, 84; respirations, 20; blood pressure, 130 systolic, 70 diastolic. There was some pallor of the mucous membranes. The head and neck presented no abnormalities. The lungs were clear to auscultation and percussion. The heart sounds were of good quality; there were no enlargement and no murmurs. The abdomen disclosed no masses or tenderness. There was a distinct pallor of the mucous membranes of the vagina and there was moderate vaginal bleeding. The uterus was soft and enlarged to the size of a six weeks' gestation. A few irregular prominences could be palpated on its surface. The cervical canal was patulous and a small polypoid structure, the size of a pea, could be seen in the canal. This was removed and sent to the laboratory for pathological examination.

*Laboratory data.* Blood: hemoglobin, 46 per cent; red blood cells, 2,600,000 with marked achromia and polychromasia; white blood cells, 11,300 with a normal differential. Urinalysis, negative. The blood Wassermann reaction, negative. The spinal fluid Wassermann, globulin and colloidal gold tests, negative. X-ray of the chest and skull revealed no abnormalities.

The fragment of tissue removed from the cervical canal was reported: "Single unusually large fetal villus showing conspicuous Langhans cell proliferation with many mitoses" (fig. 1). The urine pregnancy test was positive. Since this report was based on the standard rat technique, using 5.0 c.c. and 8.0 c.c. of urine in the test animals, further studies were carried out and it was found that while 1.0 c.c. and 0.5 c.c. of urine also gave positive results, 0.1 c.c. of urine did not evoke a positive response. 8.0 c.c. of the patient's spinal fluid was also injected into a 50 gram rat and this, likewise, gave negative result.

*Course.* The history, physical examination, and laboratory data indicated that this was probably a chorionepithelioma of the uterus. Radical surgery was considered as the therapy of choice and the patient was transfused to overcome her anemia in preparation for operation.

*Operation.* (March 2, 1946) To minimize the possibility of spread of the neoplasm there precautions were taken: The cervix was packed with iodoform gauze and the cervical canal closed with heavy silk; the distal portions of both Fallopian tubes were likewise secured by silk ligature to obviate intraperitoneal spread; and the uterus itself was not touched during the course of the operative procedure—traction was exerted by clamps applied to the round ligaments—minimizing the possibility of trauma and spread of the tumor tissue during the operation.

The uterus presented a few small superficial myomata, was congested and enlarged to the size of a six to seven weeks' gestation. There was no evidence of spread of the neoplasm to the adjacent pelvic structures and the liver was normal to palpation. Total hysterectomy and bilateral salpingo-oophorectomy was performed.

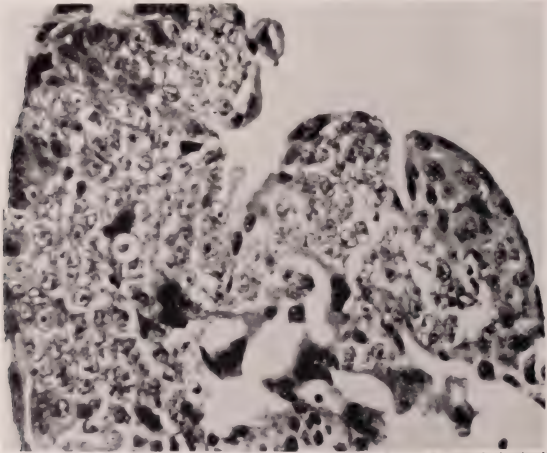


FIG. 1. Microphotograph of tissue removed from cervical canal. Pathological report: "Single unusually large fetus villus showing conspicuous Langhans cell proliferation with many mitoses."

*Pathological report.* "Specimen (fig. 2) is a totally amputated uterus with both adnexae attached. The uterus is moderately enlarged and measures 10.5 cm. in length and 6.4 cm. between the tubal angles. From the fundus arises a cherry-sized, encapsulated fibrous tumor. In the posterior wall there is another subserous fibrous tumor 2 cm. in diameter, which on section shows the whorled appearance, typical of fibromyoma. The consistency of the myometrium is softer than usual. The myometrium is 2 cm. thick, has a pale tan color and shows prominent vascular markings. The endometrial cavity is dilated. From the posterior wall and from the left side of the fundus a polypoid tumor mass arises and fills the endometrial cavity. This tumor is markedly hemorrhagic in character, its surface is partially ulcerated and covered with a gray necrotic material. The base of the tumor measures up to 5 cm. in diameter. From its lower edge a pedunculated, soft, polypoid structure which is likewise hemorrhagic, hangs down into the lower portion of the endometrial cavity. The remaining endometrium is thin, pink, and rather smooth. The cervical os shows a tear but is otherwise smooth and pale. The endocervical canal is dilated, the endocervix is smooth and pink. The left tube is 8 cm. long, the fimbrial extremity is



FIG. 2. Gross specimen of uterus opened to show polypoid tumor mass filling the endometrial cavity.

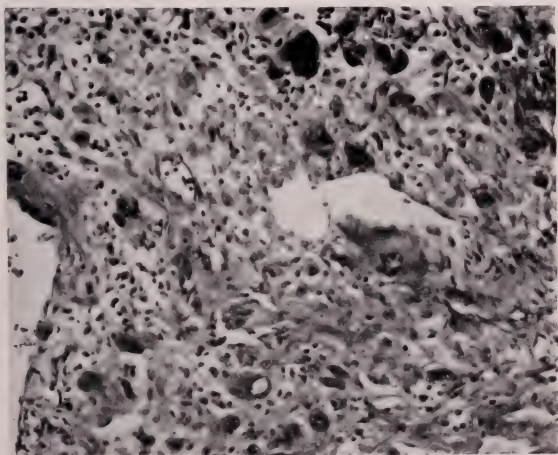


FIG. 3. Microphotograph of chorionepithelioma showing predominant invasion by syncytial elements.

patent. The left ovary has a yellowish-tan gyrated surface. Cut surface shows atrophic ovarian tissue. The right tube is 8.5 cm. long, its fimbrial extremity is likewise patent. A small 5 mm. node arises from its surface which is moderately soft and on section shows abundant lutein tissue. The remainder of the ovary likewise is atrophic." Microscopic diagnosis: "Uterus showing chorionepithelioma. Predominant invasion is by syncytial elements (fig. 3). Corpus Luteum of ovary."

*Postoperative course.* The patient's convalescence was uneventful; the wound healed by primary union, and she was out of bed on the eighth day after operation.

March 7, 1946 (5 days after operation):

Rat pregnancy test positive with 5.0 c.c.

March 14, 1946 (12 days after operation):

Rat pregnancy test positive with 5.0 c.c.

Rat pregnancy test negative with 1.0 c.c.

Rat pregnancy test negative with 0.5 c.c.

March 19, 1946 (17 days after operation):

Rat pregnancy test negative with 10.0 c.c.

Rat pregnancy test negative with 5.0 c.c.

Rat pregnancy test negative with 1.0 c.c.

The patient has been examined in the Follow-up Clinic and has remained in good health to date. The pelvis is clear, neurological examination has remained normal, x-rays of the chest show no metastases, and repeated pregnancy tests have remained negative.

#### DISCUSSION

In this case the diagnosis was made on the clinical and the pathological data. The quantitative pregnancy test, although positive, did not exceed the high levels that have been demonstrated in normal early pregnancy [Evans and his coworkers (1), Browne and Venning (2), and Schoenek (3)]. It is worthy of emphasis that the degree of malignancy is not necessarily reflected by the intensity of the pregnancy reaction. This fact has been demonstrated by Frank (4) in his series, recording a positive reaction with 0.0025 c.c. of urine from a patient with hydatid mole, while a case of chorionepithelioma with metastases required 10.0 c.c. of urine to evoke a positive response. Boycott and Smiles (5) have indicated the possibility of erroneous conclusions, based solely on the pregnancy test, because of the "overlap" of normal and abnormal ranges.

Another point of interest is the fact that the cerebrospinal fluid gave a negative reaction in this case. It has been suggested that cerebrospinal fluid from patients with chorionepithelioma produces a positive pregnancy test, whereas in hydatid mole this fluid, rarely, and in normal pregnancy never gives a positive result. We have recently encountered a case of hydatid mole (6) in which 8.0 c.c. of the cerebrospinal fluid gave a positive pregnancy reaction. The diagnosis cannot be based on one criterion alone but requires the combination of clinical, pathological, and laboratory findings to be certain.

Significant also is the fact that, despite the radical operation, the urine pregnancy test remained positive for at least 12 days after removal of the uterus and adnexae. Rubin (7) has described two cases of chorionepithelioma in which the test became negative within five days after operation. Payne (8), admitting that most cases become negative within thirty days, reported a positive reaction persisting for six months after operation. Payne felt that local, unrecognized

residual disease or distant metastases undergoing spontaneous regression after removal of the primary tumor explained the persistent positive reaction.

Finally, it is to be emphasized that measures must be taken to avoid the spread of this highly malignant tumor by special care in closing the cervix and tubes and then removing the uterus by "non-traumatic" technique and with a minimum of manipulation.

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# NEOPLASM OF A SUPERNUMERARY OVARY

## REPORT OF TWO CASES

BRUNO R. KRISS, M.D.

(*New York, N. Y.*)

Supernumerary ovaries have been found in the frog (9), in the baboon (2) and in other animals. It is not a rare finding in the human; in 500 autopsies Beigel (12) discovered 23 cases of accessory ovaries, v. Winkel (11) 18 cases in his material of 500 cases. Rieffel reported an incidence of 4 per cent in his material.

Supernumerary ovaries are of considerable embryological importance and clinical significance. Their presence explains the occurrence of menstruation, ovulation and even conception after bilateral oophorectomy (8). Seitz (quoted by Miller), Stolz (10) and Engstroem (4) discussed the embryological development of this condition and divided the cases into 3 groups:

*Group I. Cases derived from a third gonadal primordium.* In such cases supernumerary Fallopian tubes may be present. Occasionally, there is only a supernumerary band (a ligamentum ovarii propr.). Stolz (10) includes in this group cases in which a supernumerary tube or a supernumerary band is absent. The supernumerary ovary of this group is called "ovarium tertium." Kermauner (7) doubts the existence of this group.

*Group II. Cases derived from one of the two gonadal primordia.* At a very early embryological stage (stage of the gonadal crest) a portion of one anlage is split off and develops into a separate ovary, called by Beigel (12) accessory ovary. It is often connected by a short pedicle to the hilum of a normal ovary at the Farrè-Waldeyer line.

*Group III. Cases derived from one of the two gonadal primordia.* These anlagen are already well differentiated. Due to pathological processes occurring during late fetal life the gonad is split into two or more parts, which give rise to the so-called *ovarium partitum*, or *ovarium disjunctum* (Schottlaender), or *ovarium lobatum* (v. Rosthorn), or *ovarium succenturiatum*. The ovary may be split either completely or partially and the portions connected by fibrous tissue.

Cases belonging to the first group are rare. V. Winkel described a case where a third ovary was situated in front of the uterus and attached to it by a ligament. Keppler (6) reported a case with 3 ovaries and 3 Fallopian tubes. However, the greatest number of reported cases apparently belong to group II or III.

Miller (8) has written extensively on supernumerary ovaries. He has classified tumors occurring in such ovaries as follows: 1. Neoplasm in the supernumerary ovary in the presence of two normal ovaries; 2. Neoplasm in the supernumerary ovary and neoplasm in one ovary in the presence of one remaining normal ovary; 3. Neoplasm in the supernumerary ovary and in both ovaries; 4. Neoplasms in two supernumerary ovaries combined with neoplasms in both ovaries.

In most of the cases of Miller's classification a ligament connecting the third ovary with the uterine fundus is described. Frank (5) reported an exceptionally

rare case of an ovarian tumor in combination with a neoplasm of a supernumerary ovary where a third Fallopian tube was present.

The following two cases are instances of neoplasm in a supernumerary ovary. The tumors were found accidentally in the course of a laparotomy.

#### CASE REPORTS

*Case 1. History.* (Adm. #55139) K. B., aged 49 years, grav. III, para III, was admitted to the Manhattan General Hospital on November 13, 1944, complaining of pain in the right lower abdomen, severe menorrhagia, constipation and frequency of urination for 14 months. The menses were previously normal (13 x 28 x 5).

*Examination.* The patient was a slender woman, who appeared well. On abdominal palpation a soft irregular mass arising from the pelvis could be felt. Gynecological examination revealed a parous introitus, an eroded lacerated cervix and a uterus irregularly enlarged to the size of a four months gestation. The enlargement was due to several nodules varying in size from 2 to 7 cm. in diameter. One of these nodules situated in front and to

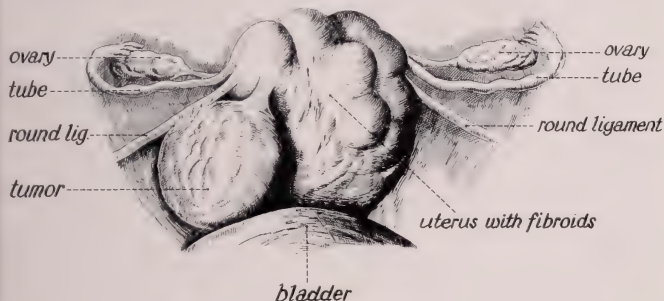


FIG. 1

the right side of the uterus was very soft and tender. Both ovaries were palpable but normal in size (fig. 1).

*Course.* Laparotomy performed on November 14, 1944, showed the uterus to be enlarged by several intramural and subserous fibromyomata. In front and to the right side of the uterus a soft mass, about the size of an orange, was found (fig. 1). The round ligament crossed the lateral surface of this tumor and was intimately adherent to it. There was also a fibrotic band, 2 cm. long, connecting the uterine fundus with the mass. The ovaries and tubes were normal. This mass, which appeared to be a soft degenerated fibroid, was removed, and in addition a total hysterectomy was performed, leaving the ovaries and tubes. The pathological report of the specimen was as follows: "1. Fibromyomata uteri. 2. For the tumor mass the predominant histologic picture in all slides examined was that of large diffuse fields of somewhat immature granulosa cells with no definite suggestion of a folliculoid pattern anywhere. The cells were not clearly outlined, the nuclear content was variable, and an occasional mitotic figure was present. The connective tissue stroma, where present, was scant. In field after field it was lacking altogether. Diagnosis: Granulosa cell carcinoma of the ovary." The post-operative course was uneventful. The patient received post-operative radiotherapy. Eighteen months after the operation the patient was well and the gynecological examination revealed both ovaries palpable and normal.

*Comment.* The location of this neoplastic ovary in front of the uterus and separated from the right ovary by the broad ligament favors the derivation from a third gonadal anlage rather than its origin from one of the two normal anlagen. The presence of the small band between the uterine fundus and the tumor (lig. ovarii propr. tertium?) confirms the assumption that this case apparently belongs to the embryological group I. V. Winkel described a case similar to this one except that the supernumerary ovary was normal.

*Case 2.<sup>1</sup> History.* (Adm. #C6146) O. S., aged 34 years, grav. O, para O, was admitted to the West Side Hospital on October 26, 1943, complaining of pain in the left lower abdomen of six years duration. The menses were normal (13 x 28 x 3). The past history was essentially negative. The patient was rejected from the Women's Army Corps in 1942 because of a pelvic tumor.

*Examination.* The general physical examination showed a young woman not apparently ill. The abdomen was markedly distended. The gynecological examination revealed a nulliparous normal vulva and vagina. The uterus was anterior, normal in size and contour, but somewhat soft and pushed to the left side by a cystic mass the size of a man's head which could be felt at the right side of the uterus. The left ovary could not be palpated.

*Course.* At laparotomy on October 27, 1943, a large cyst was found which apparently developed in an accessory ovary of the right side. The right ovary which was completely separated from the tumor, rested on the posterior surface of the broad pedicle of the cyst and appeared normal. After ligating and cutting the pedicle lateral to the right ovary the cyst was extirpated. The Fallopian tube, which ran on the upper rim of the pedicle and over the top of the cyst was 20 cm. long and was partially resected. At the hilum of the left ovary a small cyst was enucleated. After the operation the patient still had two normal ovaries, one normal tube, one partially resected tube, and a normal uterus. Pathological diagnosis: large serous cyst adenoma of the ovary. The postoperative course was uneventful.

*Comment.* Since this case does not show a supernumerary Fallopian tube or a supernumerary ligament between tumor and uterus nor a pedicle connecting the neoplastic ovary to the right ovary, the embryological origin of this case must be placed into group III. The serous cyst adenoma of this patient apparently had developed in the lateral portion of an "ovarium disjunctum" dextrum.

An interesting fact concerning the location of supernumerary ovaries is that they usually occur on the right side. This is demonstrated by the majority of the cases reported in the literature and also found in the two cases presented. Stolz (10) emphasized this point long ago and felt that this is not a mere coincidence. There seems to be a definite tendency for congenital abnormalities to occur more often on the right side in both the human and the animal pelvis. For instance, the right ovary of the hen is normally rudimentary and sometimes develops into a testis if the normal left ovary is removed [Benoit (1), Domm (3)]. Also in cases of unilateral aplasia ovarii the right side is more often affected than the left side. The incidence of ovarian dermoids on the right side is higher than on the left side. Among 805 ovarian dermoids Miller (8) found 431 on the right and 347 on the left.

These facts have a definite clinical significance. If an ovary or a pelvic neo-

<sup>1</sup> This case is reported through the courtesy of Dr. Joseph Novak of New York City, to whom I extend my sincere thanks.

plasm is found in an unusual location on the right side, the possibility of a third ovary must be considered. This conclusion would have been of great help in establishing the correct diagnosis in Case 1.

## SUMMARY

Two cases are reported in which a neoplasm developed in a supernumerary ovary. In both cases the condition occurred on the right side. The first case was that of a granulosa cell carcinoma in a third ovary, situated in front and on the right side of a fibromyomatous uterus and attached to this organ by a short fibrotic band. The second patient had a serous cystadenoma of an ovarium disjunctum dextrum, together with a small cyst of the left ovary. The origin and the clinical aspects of both cases are discussed.

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# EXTRAGENITAL DISEASE IN THE GYNECOLOGICAL PATIENT

LOUIS S. LAPID, M.D.

(New York, N. Y.)

*From the Gynecological Service of The Mount Sinai Hospital, New York, N. Y.*

This report covers 206 patients who, in addition to their gynecological complaints manifested co-existing serious dysfunctions which were ignored by the patient and were unknown to the referring physician. This collection of cases constitutes 2.6 per cent of a total of 7,712 admissions to the Gynecological Service at The Mount Sinai Hospital during a period of ten years. It is divided into two groups: (Group I) 72 cases, whose symptomatology and pelvic findings were masked by genital tract dysfunction and in whom no organic disturbances of the reproductive organs were present, and 134 cases (Group II) who, on more thorough investigation exhibited independent extragenital conditions in addition to disturbances of the genital tract.

## GROUP I

*Conditions simulating genital tract dysfunctions.* The admission diagnosis with which these 72 patients entered the hospital included acute and chronic pelvic inflammatory disease, menstrual disturbances, fibromyomatous uteri, ovarian tumors and rectovaginal fistulae. Symptomatology and physical findings of this group could be construed as gynecological in nature; nevertheless, after investigation, the extragenital site of the disease was discovered.

*Intestinal tract.* A patient presenting the physical findings of chronic pelvic inflammatory disease should arouse the suspicion of intestinal tract involvement for as it has so often been said, every diagnostic procedure must be employed to exclude the possibility of an extragenital cause of pelvic inflammation.

Sigmoidal carcinomata and diverticulitis of the colon were the most frequent lesions simulating pelvic inflammatory disease (Table I). Although malignancies were usually encountered in patients in their fourth to sixth decade of life, a carcinoma of the sigmoid was discovered in a young woman, aged 22 years, who was referred into the hospital with a diagnosis of an ovarian tumor with associated pelvic inflammatory disease. Another patient, aged 24 years, had an adenocarcinoma of the rectum and was treated for a rectovaginal abscess.

*Genito-urinary tract.* Eight cases of ectopic kidneys were referred into the hospital as "ovarian tumors." These patients complained of lower abdominal pain and backache. Tumor masses were palpable in the pelvis. The diagnosis of pelvic kidney should be suspected if (1) there is a rubbery consistency to a tumor on pelvic examination, and (2) the tumor is more easily defined on rectal examination than on vaginal examination. The final established diagnosis is made by intravenous or retrograde pyelography.

Three cases of large cystic kidneys were admitted to the Gynecological Service; two were diagnosed as pedunculated fibromyomata uteri, and one as an ovarian tumor.



*General medical disorders.* Two patients were referred to the hospital as acute pelvic inflammatory disease. One was found to have malaria, the other acute infectious mononucleosis. Another patient with typhus fever complained of a profuse vaginal discharge with hyperpyrexia. Hypothyroidism was the final diagnosis in two cases of secondary amenorrhea, and in four patients who complained of menometrorrhagia. Four of this group received estrogen therapy because of their menstrual irregularities.

*Neurological disorders.* In four cases of urinary incontinence there were manifestations of central nervous system disease: three had tabes dorsalis and one multiple sclerosis. All had been observed and treated by their physicians with pessaries and local bladder therapy.

TABLE I

FINAL DIAGNOSIS	NO. OF CASES
Carcinoma of cecum.....	2
Carcinoma of sigmoid.....	6
Carcinoma of rectosigmoid.....	3
Carcinoma of rectum.....	1
Intestinal actinomycosis.....	1
Granuloma of cecum.....	1
Diverticulitis of sigmoid.....	8
Diverticulitis of ascending colon.....	1
Perforating diverticulitis of sigmoid with abscess formation.....	2
Inflammatory non suppurative sigmoiditis.....	1
Lymphopathis venerium with rectal stricture.....	2
Incarcerated femoral hernia.....	1
Incarcerated ventral hernia.....	1
Hematoma of left rectus abdominal muscle.....	1
Total.....	31

One patient complaining of amenorrhea, pelvic discomfort, and failing vision of fifteen months' duration was being treated with hormonal therapy. Perimetric studies revealed bilateral visual field defects. In view of the above findings, the patient was transferred to the Neurological Service where she was subsequently operated upon for a suprasellar meningioma.

*Psychiatric disorders.* Signs and symptoms presented by the psychoneurotic patients were numerous, protean, and kaleidoscopic. Such patients, when sent into the hospital from the Out Patient Clinic, invariably had records revealing that they had attended almost every Out Patient Department.

Seven cases of psychoneurosis, mixed type, and eight cases of conversion hysteria were diagnosed in patients having gynecological complaints. Conditions as amenorrhea, menometrorrhagia, incontinence, pruritus vulvae, leucorrhea, sterility, etc., may present themselves as psychic conflicts. Still, one must exclude organic lesions which may be present as a causative factor in any of the above conditions. To cite a case in point:

Mrs. R. was referred to the Consultation Clinic because of a severe psychoneurosis with incidental menometrorrhagia which seemed to her to vary with her mental state. An early endocervical carcinoma was discovered.

#### GROUP II

Multiple diagnoses of serious nature were made in 134 cases. Many of these cases had no gynecological surgery performed because the new findings were considered more significant than the original pelvic disorder. The extragenital conditions will be presented according to the service to which the patients were referred.

*General surgical disorders.* 38 cases were referred to the General Surgical

TABLE II

FINAL DIAGNOSIS	NO. OF CASES
Fibrosarcoma of stomach.....	1
Carcinoma of stomach.....	2
Carcinoma of ascending colon.....	1
Carcinoma of transverse colon.....	1
Carcinoma of splenic flexure.....	1
Regional ileitis.....	1
Fibroma of cecum.....	1
Intestinal obstruction.....	1
Inguinal herniae.....	16
Femoral hernia.....	3
Cholelithiasis.....	3
Carcinoma of gallbladder.....	1
Hydrops of gallbladder.....	1
Pancreatic cyst.....	1
Hyperthyroidism.....	2
Fibroma of breast.....	1
Intracannillicular fibroma of breast.....	1
Total.....	38

Service. Table II shows the conditions which were present in addition to the gynecological disorders.

#### ILLUSTRATIVE CASES

*Case 1.* Mrs. P. Z., aged 39 years, was treated by her physician for menometrorrhagia for six months. Pelvic findings were always negative. In the hospital, symptoms referable to the gastro-intestinal tract were noted. The guaiac stool test was positive. X-ray studies revealed a filling lesion of the stomach. The diagnosis of carcinoma of the stomach and menometrorrhagia was made.

*Case 2.* Mrs. M. G., aged 49 years, entered the hospital for a hysterectomy, because of a fibroid uterus. One year before admission she was advised that an operation would be unnecessary since the fibromyoma would decrease in size with the onset of menopause. But, because of the persistence of right lower quadrant pain, she was hospitalized. Stool guaiac test was positive; barium enema revealed a filling defect of the ascending colon. A carcinoma of the ascending colon and fibroid uterus was the diagnosis.

*Co-existing genito-urinary conditions.* Nineteen cases of genito-urinary and gynecological dysfunctions were present. As noted in Table III, some of the

genito-urinary tract pathology were very severe, while other conditions were moderately severe.

TABLE III

FINAL DIAGNOSIS	NO. OF CASES
Malignant Grawitz tumor of kidney.....	2
Tuberculosis of kidney.....	1
Renal calculus.....	4
Ureteral calculus.....	1
Bladder calculus.....	1
Bladder carcinoma.....	1
Hydronephrosis.....	9
Total.....	19

TABLE IV

FINAL DIAGNOSIS	NO. OF CASES
Gastro-intestinal	
Duodenal ulcer.....	6
Gastric ulcer.....	2
Chronic pancreatitis.....	1
Hiatus hernia.....	1
Cholecystitis.....	8
Cholelithiasis.....	4
Hepatosplenomeglia (etiology unknown).....	1
Cardiovascular	
Coronary thrombosis.....	4
Syphilitic aortitis with aneurysm of subclavian artery.....	1
Pulmonary	
Bronchiectasis.....	9
Pulmonary tuberculosis.....	6
Metabolic	
Hyperthyroidism.....	14
Diabetes mellitus.....	2
Amyloidosis, primary.....	1
Bone diseases	
Paget's disease.....	1
Blood diseases	
Polycythemia vera.....	3
Pernicious anemia.....	3
Multiple myeloma.....	2
Total.....	69

## ILLUSTRATIVE CASES

*Case 1.* Mrs. B. B., aged 48 years, was observed by her doctor for a "fibroid uterus with a pedunculated fibroid." She entered the hospital because of increasing abdominal enlargement of the tumors and menometrorrhagia. Because of the position of the "pedunculated fibroid" in the left upper quadrant of the abdomen, an intravenous pyelogram

was done. This revealed a lesion of the left kidney. The diagnosis was a malignant Grawitz tumor of the left kidney and a fibroid uterus.

*Case 2.* Mrs. M. S., aged 34 years, was referred to the hospital for removal of a fibromyomatous uterus. Her history revealed occasional dysuria and night sweats. Urinalysis showed microscopic pyuria and hematuria. A pyelogram revealed "moth-eaten calyces." Diagnosis: Tuberculosis of right kidney and fibroid uterus.

*General medical disorders.* In this study, 69 patients had general medical disorders. Many of these cases were operated upon because of the severity of their gynecological complaints. These cases were either transferred to the medical service following surgery, or following the transfer they were returned to the Gynecological Department when their physical condition warranted surgical intervention. Table IV is subdivided into topographical symptoms according to diagnosis.

#### ILLUSTRATIVE CASES

*Case 1.* Mrs. B. L., aged 42 years, was referred to the hospital by her physician for hysterectomy for fibroid uterus. The patient complained of pain in her lower spine and menorrhagia. Physical examination revealed local bone tenderness and low back pain on motion. Pelvic examination revealed a small fibromyomatous uterus. X-ray of the bones was taken, and sternal marrow blood studies were performed. Multiple myeloma and fibroid uterus was the diagnosis.

*Case 2.* Mrs. A. Y., aged 43 years, was referred to the hospital because of a fibromatous uterus. She complained of menorrhagia, and substernal and epigastric pains of one month duration. Electrocardiogram was done. Final diagnosis: Myocardial infarction and fibroid uterus.

*Orthopedic disorders.* Backache is a common gynecological complaint. Eight cases of spondylitis are reported here for the reason that in addition to the presenting gynecological dysfunctions, these patients had (1) x-ray findings of bone changes which were severe enough to be able to cause the presenting symptom, (2) orthopedic examination which revealed positive signs (local tenderness, Lagnere's and Goldthwaite's signs) that were indicative of spondylitis.

#### SUMMARY

1. There were 7,712 admissions to the Gynecological Service of The Mount Sinai Hospital during a ten year period beginning July 1, 1936.

2. Two hundred and six patients (2.6 per cent) had in addition to their gynecological complaints co-existing serious extragenital dysfunctions.

3. Seventy-two patients had symptoms and findings of pelvic involvement, masked as genital tract dysfunctions and in whom no organic disturbances of the reproductive tract were present. They included: a. Carcinoma of the large bowel, and diverticulitis of the sigmoid. b. Pelvic kidneys, thought to be ovarian tumors. c. Urinary incontinence, as a manifestation of disease of the central nervous system. d. Psychoneurosis in patients with multiple complaints presenting a bizarre picture.

4. One hundred and thirty-four cases are presented in whom there were serious independent extragenital conditions in addition to disturbances of the reproductive tract.

## UTERUS DIDELPHYS WITH ENDOMETRIAL POLYP IN LEFT UTERUS

MAURICE E. MINTZ., M.D.

(New York, N. Y.)

The incidence of congenital malformations of the female genital tract is much more common than is generally appreciated. Most abnormalities are discovered during the course of exploratory laparotomies, or through uterosalpingography, as in the following case.

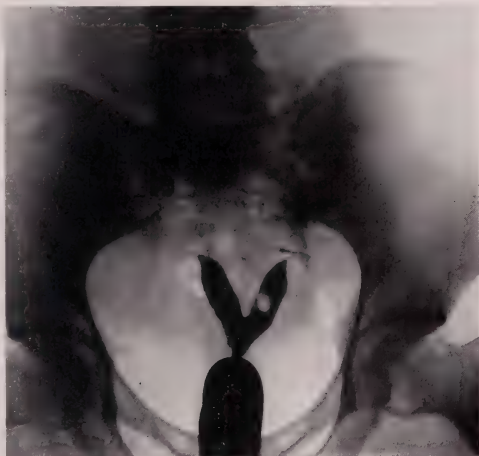


FIG. 1

*History.* J. P., age 33, unmarried, para 0, gravida 0. Menses began at 13 years, and occurred every 28 days, lasting 4 days with severe cramps the first 2 days. Last normal period was October 5-9, 1943. The patient presented herself for treatment on November 5, 1945, with the complaint of severe dysmenorrhea ever since the onset of menstruation, and bleeding almost daily for the past 2 years. She was given estrogens, proluton and snake venom during the 2 years, without any effect on the bleeding.

*Examination.* The patient was a rather short stout woman weighing 160 pounds. Her voice was rather hoarse, and she had some hair on the face and chest, and her pubic hair was of the male type distribution. Her breasts were large and well developed.

The external genitals were normally developed, and the hymen was intact. On rectal examination the cervix felt normal, the fundus could not be outlined due to obesity and involuntary rigidity.

*Laboratory data.* The urine examination was negative. The blood study showed 4,600,000 red blood cells; hemoglobin 95 per cent; color index, 1.02; leucocytes, 12,150; neu-





FIG. 2

trophiles, 55; segmented 53; staff, 2 per cent; eosinophiles, 3 per cent; lymphocytes, 32 per cent; monocytes 10 per cent. The basal metabolism, plus 14 per cent.

*Course.* A hystero-gram (fig. 1) performed on November 17, 1946 was reported as: "Utero-salpingography revealed a double uterus and a single cervix. In the center of the left uterine cavity was a filling defect, about one centimeter in diameter. This is most likely an endometrial polyp. Both tubes were visualized to the fimbriated extremity and appeared normal."

On December 15, 1945, patient was operated upon at The Mount Sinai Hospital. The endometrial polyp was removed and the left uterine cavity thoroughly curetted.

The removed polyp was reported by the pathologist as showing: "Fragments of endometrium in a proliferative phase; fragments of a partially necrotic endometrial polyp."

Two months after the operation another hystero-gram was performed and showed both uterine cavities to be normal (fig. 2); the defect which was present in the left uterine cavity, with the removal of the polyp, disappeared.

The patient made an uneventful afebrile recovery and left the hospital on December 23, 1945. Her periods have been normal since the operation, occurring every 28-30 days with much less pain and only on the first day of the period.

# RUPTURED DERMOID CYST

## CASE REPORT

CHARLES S. POOLE, M.D.

(New York, N. Y.)

*From the Gynecological Service of The Mount Sinai Hospital, New York, N. Y.*

Dermoid cysts are a fairly common type of ovarian tumor and, according to the literature, comprise 10 to 35 per cent of all ovarian tumors. In most instances they are asymptomatic, except for mild pressure symptoms, and are often discovered in the course of a routine pelvic examination or x-ray of the abdomen. They are usually slow growing and seldom give rise to symptoms unless complications occur. The complications to which they are subject are (1) torsion, (2) hemorrhage, (3) suppuration, (4) malignant degeneration, and (5) rupture.

In a series reported by Lippert, 4.5 per cent of the dermoid cysts studied ruptured. According to this report, rupture of a dermoid cyst would seem to be a not too uncommon occurrence. This, however, has not been our experience.

The following case is presented to illustrate this complication and the difficulties encountered in diagnosis.

## CASE REPORT

*History.* (Adm. #495836) A white female, aged 64, was admitted to the medical service on September 29, 1942, complaining of abdominal pain, vomiting and diarrhea. Because of language difficulty, the history was inadequate. The patient had been in good health until the present illness. The menopause occurred spontaneously twenty years previously and there had been no bleeding since. Eight days prior to admission she developed crampy abdominal pain accompanied by vomiting and diarrhea. She had 8 to 10 watery stools daily which contained no pus, blood or mucus. For the first few days the patient's temperature rose to 101° F. She had no chills. With the return of normal temperature she was still vomiting and diarrhea persisted.

*Examination.* The patient was a dehydrated and cachectic elderly female. The abdomen was distended and there was some tenderness to the right of the umbilicus. A smooth liver edge was palpable one finger breadth below the costal margin. The spleen was not palpable. There was no evidence of free fluid in the peritoneal cavity. Pelvic examination revealed a large, smooth, nontender mass, the size of a grapefruit, filling the cul de sac. The fundus was not distinguishable. Rectal examination revealed no palpable mass within the rectal lumen. The temperature on admission was normal. She exhibited evidences of generalized arteriosclerosis. Her blood pressure was 135 systolic and 80 diastolic.

*Laboratory data.* The hemoglobin was 73 per cent, red blood cells 4.3 million, white blood cells 21,700 with 90 per cent segmented forms, 9 per cent non-segmented, and 1 per cent monocytes. There was slight toxic granulation. The sedimentation rate was 18 mm. in 21 minutes. Blood urea nitrogen was 21, total protein 7, sugar 145, cholesterol 140 and CO<sub>2</sub> 49.5 vol. per cent. The Wassermann was negative. The stool was mustard colored and guaiac negative. The electrocardiogram showed no abnormality. A barium enema showed no organic lesion in the colon. The rectum and sigmoid were displaced to the left by a pelvic mass which extended into the abdomen. X-ray examination of the chest showed no abnormality of the lungs. Both leaves of the diaphragm were elevated.

*Course.* On admission it was thought that the patient might be suffering from a colonic

neoplasm, and coincidentally had a fibroid uterus. To combat the dehydration and avitaminosis the patient was treated with intravenous glucose in saline and large doses of vitamins. She also received transfusions of whole blood.

The patient was seen by the gynecologist and it was noted that the cervix was small and crowded forward under the symphysis. Behind was the lower pole of a large tense mass, fixed but not tender. The mass extended upwards into the abdominal cavity and seemed to contain fluid. The upper limits could not be defined. The possibility of an ovarian malignancy was entertained. It was suggested that a laparotomy be performed as soon as the patient was considered in suitable condition.

On her second day in the hospital a fluid wave was noted. A peritoneal aspiration was performed and 50 cc. of milky white fluid, containing many fat droplets were obtained. The specific gravity was 1.020, the protein was markedly increased, but no organisms were found either on smear or culture. Due to the nature of the fluid, chylous ascites was considered and believed to be due to a metastatic neoplasm causing pressure on the thoracic duct or receptaculum chyli. The fluid in the abdomen increased, the distention became more marked, and the course was rapidly downhill. Because of the lack of response to medical therapy, the patient was transferred to the gynecological service for surgery. The patient was in extremis, disoriented, distended, and the abdomen was rigid throughout. The temperature remained normal. A ruptured dermoid cyst was suspected as the pelvic mass was associated with a rapidly accumulating milky abdominal fluid producing an irritative peritonitis.

On October 10, an exploratory laparotomy was performed under field block anesthesia. On opening the abdomen it was found to be filled with creamy cheesy yellowish fluid in which hair was floating. She was then further anesthetized with cyclopropane and oxygen. The fluid was removed and in the left broad ligament a multiloculated grapefruit sized cyst was found. One of the loculations was collapsed and an opening noted on its surface. The left tube and ovary with the attached cysts were removed. The abdominal cavity was drained transabdominally and the abdomen was closed in layers reinforced with through and through sutures.

*Pathological report.* The specimen consisted of a resected multiloculated ovarian cyst and tube. The tube measured 5 cm. in length and could be probed readily. The attached ovarian mass measured approximately 14 x 10 cm. and had been opened. There was hair and yellowish cheesy material on the external surface as well as within the specimen. The contents of all of the cysts was smooth lined except for one area where there was a papillary skin like projection from which hair arose. There also was an area of calcification resembling a tooth. The microscopic diagnosis was dermoid cyst.

The postoperative course was very stormy. The patient developed congestive heart failure with auricular fibrillation. She was digitalized rapidly by the intravenous route and placed in an oxygen tent. She responded very slowly and convalescence was prolonged. She developed a decubitus ulcer, was disoriented, became incontinent of urine and feces, and required constant nursing care. Her temperature was normal except for an occasional rise to 101° F. Recovery was slow. The wound healed, the decubitus ulcer responded very sluggishly to therapy but finally healed, her cardiac rhythm returned to normal, she became oriented, was no longer incontinent, and by December 14, two and a half months after admission, was in condition for transfer to a convalescent home. She has remained well and is in good health at present, three years after operation.

*Comment.* In reviewing the number of dermoid cysts encountered on the gynecological service of this hospital in the last 13 years, it became apparent that rupture is an extremely rare complication. Of 133 cases of dermoid cyst, rupture was encountered only once, an incidence of 0.7 per cent. It usually results from trauma, pressure, torsion, vascular accident or infection. The rupture can occur into the peritoneal cavity, as in this case, and cause an irritative peritonitis.

When rupture occurs it usually is an emergency. However, it may occur slowly and small amounts of buttery dermoid material from pea sized to walnut sized, with or without hair, may become encysted in the peritoneum. These peritoneal implants may become calcified. Implants are sometimes mistaken for dermoid metastases.

Rupture may also occur into a hollow viscus such as the bladder, vagina, uterus or intestines. In such event the dermoid contents can be found in the excretory passage of the particular organ involved. Perforation has also been reported to occur through the abdominal wall.

As regards the etiology in this case, trauma, torsion or vascular accident are all possibilities. However, pathological study of the resected specimen excludes the two latter possibilities. There was no history of trauma. Unfortunately the language difficulty in obtaining an accurate history precluded an exact evaluation. However, it would seem that this is an instance of spontaneous rupture of a dermoid cyst.

In arriving at a diagnosis, the peritoneal aspiration of milky fat fluid made it necessary to exclude the possibility of chylous ascites and the various causes for such a condition.

#### CONCLUSIONS

1. Rupture of a dermoid cyst of the ovary, simulating a chylous ascites is reported.
2. The poor condition of the patient did not exclude the possibility of cure by surgery.
3. Rupture of a dermoid cyst is an extremely rare complication of this type of ovarian tumor.

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## DIAGNOSTIC AND SURGICAL PROBLEMS ENCOUNTERED IN SOME MALFORMATIONS OF THE FEMALE REPRODUCTIVE SYSTEM

MEYER D. SCHNALL, M.D.\*

(New York, N. Y.)

*From the Gynecologic Service of the Mount Sinai Hospital, New York*

The internal reproductive system of both male and female arise from the urogenital folds which are a bilateral mass of cells present on the posterior wall of the embryo. The urogenital folds give rise to the Mullerian ducts, Wolffian bodies, Wolffian ducts, and the ovary or testicle. The Mullerian ducts develop into the Fallopian tubes, uterus, and upper vagina. The lower portion of the vagina develops from the urogenital sinus in association with the external genitalia. Early in the third month, fusion of the Mullerian ducts begins and the septum formed by their united walls disappears in a caudocranial direction, thus creating the cavities of the vagina and uterus. Higher up, the ducts remain unfused as the Fallopian tubes. Because of this bilateral development of the tubes, uterus, and vagina the congenital anomalies may be complete or partial, bilateral or unilateral, and symmetrical or asymmetrical. The processes operating during embryonal life to produce such defects are aplasia, hypoplasia, atresia and duplication of the Mullerian ducts. Thus a woman was reported with two completely separated uterine bodies, two vaginae, two vulvae and two urinary bladders. This patient had been pregnant in each uterus. Such an anomaly is rarely seen in living human beings as there are usually other associated anomalies that are incompatible with life. On the other hand, patients have been seen with a complete symmetrical aplasia of Muller's ducts so that the tubes, uterus, and vagina are absent. Most malformations observed, however, are between these two extreme and rare conditions. Due to the intimate development of the female reproductive system with the urinary organs, abnormalities of the latter are not uncommon in the same individual.

Some of the factors which seem to be concerned with the development of such malformations are defective ova or spermatozoa and an unfavorable environment. The tendency toward the development of anomalies is hereditary. Most grossly malformed fetuses die *in utero* and are aborted. It is also recognized that the fetus is responsive to unfavorable physical and chemical influences in its environment during early embryonic life.

*Diagnosis.* Some of these anomalies are discovered by pelvic examination, by the examination of the pelvic organs during vaginal or abdominal operations, and by post mortem study. With the introduction and pioneer development by Dr. I. C. Rubin of hysterosalpingography the diagnosis of uterine anomalies has become more frequent from year to year. Also such radio-opaque study has made it possible in most cases to determine the precise anatomical variation.

\* Dr. Joseph Brettauer Fellow in Gynecology, Mount Sinai Hospital.



Obviously anomalies of the female reproductive system frequently present diagnostic, surgical and obstetrical problems. Thirty-five patients with such congenital malformations (exclusive of those with absent vagina, uterus and tubes) are described.

#### ANALYSIS OF THIRTY-FIVE CASES

I. *Uterus bicornis duplex* or *uterus pseudodidelphys* is a malformation due to faulty juxtaposition of Muller's ducts. Here there are two uterine bodies, the cervixes are joined, the vagina is double, partially septate, or single, and one of the horns in some cases is rudimentary, either solid or with a cavity. This is normal in the squirrel, hare, and beaver, animals with a single vagina. A true uterus didelphys is very rare; the bodies and cervixes are completely separated and there are separate vaginae. In about 10 per cent of these cases there is found the recto-vesical ligament, a band of peritoneum passing from the rectum to the bladder. It has been suggested that this is the cause of the anomalous development.

Twelve cases of uterus bicornis duplex came under observation. Because of the duplication of fundi, cervixes, and vaginae, recognition of the malformation was made on pelvic examination in all but one case where the hymen was intact and vaginoscopy aided in making the diagnosis. In 9 of the patients the vaginae were completely separated by a vertical septum. In two cases only the distal one-quarter of the vagina had a septum and in one the vagina was entirely single. In some of the patients only one of the vaginae was marital, the other being virginal. In other patients both vaginae were marital. They usually do not know they possess two vaginae.

The tendency toward sterility and spontaneous miscarriage is rather marked. Data is complete in ten married women of this group. Eight conceived. Five patients conceived only once and each of these terminated in a spontaneous miscarriage. One delivered two term babies, the first was a breech presentation; the second baby died five days after birth, cause unknown. One was pregnant at the time of study; she had an absent left kidney and a congenital cardiac lesion. Another patient had three induced abortions and came to the hospital to have the septum excised as she was now seriously considering carrying to term. Two patients were sterile. Five patients complained of severe dysmenorrhea. Where the data is complete, the menses were described as essentially normal in character, and regular.

Three cases of uterus bicornis duplex will be described further—one a pyocolpos, another in which a double hysterectomy was done for fibroids, and one sent to the hospital as a suspected ectopic pregnancy.

*Case 1.* A single woman, aged 25 years, was admitted to the gynecologic ward with the complaint of profuse vaginal discharge since the age of seventeen, left lower quadrant pain for one year, and a history of severe dysmenorrhea since the menarche. Four months previously urologic study revealed by intravenous pyelogram an absent kidney shadow on the left and an enlarged right kidney with good renal function. Cystoscopy showed only a right ureteral orifice, none on the left. Injected indigo-carmin appeared only from the right ureteral opening. Bacteriologic study of the discharge revealed gram-negative cocci

and no tubercle bacilli or yeast cells. Pelvic examination disclosed a profuse vaginal discharge, intact introitus and by rectal palpation the cervix felt normal, fundus could not be outlined, right adnexal region was clear and on the left an orange-sized cystic mass was outlined. Vaginoscopy with a narrow proctoscope showed one cervix with a normal os. One-half inch to the left was a sinus opening, 3 millimeters in diameter, from which thick pus exuded. Four days later menses started and vaginoscopy was repeated. Menstrual blood and pus were seen coming from this tiny orifice. Twenty-four hours later menstrual blood began to issue from the normal cervix. Through the stretched hymen a catheter was threaded into the sinus which was dilated and the cystic cavity (a pyocolpos) was irrigated. The septum of the pyocolpos was excised and the pathologist reported this to show a fibromuscular septum covered on both sides by squamous epithelium. Thereafter a small cervix could be seen; a cannula was inserted into each cervical canal and a radio-paque dye injected into both uteri, visualizing both uterine cavities and both Fallopian tubes. Fifteen days later menses began and blood was seen coming from both cervices.

*Case 2.* This patient, a woman aged 39 years, was married for twenty years without ever having conceived. Her complaint was constant left lower quadrant pain. Pelvic examination revealed tenderness in left lower quadrant, normal vulva, double vaginae, double cervix and double uterus. The adnexae were not palpable. Both uteri seemed enlarged, the left more than the right. Hysterography revealed two uterine cavities with a filling defect in the left one. At operation a typical double hysterectomy was done. Both uteri were enlarged by multiple small fibroids and on the serosal surface of the uteri was evidence of endometriosis. The above described rectovesical ligament was present in this case—the congenital band of peritoneum between the bladder and the rectosigmoid was divided. The pathology report was: uterus pseudodidelphys with small fibromyomata and endometrial polyp in left uterus; endometriosis found on the serosal surfaces.

*Case 3.* This woman, aged 26 years, was sent to the emergency room of the hospital with a diagnosis of possible ectopic pregnancy. Two days after she had expected the onset of a normal period, vaginal spotting and colicky right lower quadrant pains began. The Aschheim-Zondek Test was positive the day before. This was her first pregnancy. On pelvic examination there were found two vaginae, both marital and of equal size, separated by a septum two millimeters thick. Two cervices were exposed. The uterus on the left was small, that on the right was the size of a normal nulligravidous uterus and tender. Adnexae were not palpable. She was treated as a threatened abortion of a gestation in the right horn of a double uterus by bed rest only and was discharged when spotting subsided. Eight days later she was curetted at another hospital because bleeding started again. The report indicated that the right uterus was three inches deep and curettings showed "necrotic inflamed chorionic villi." The left uterus sounded one and a half inches deep and curettings showed "necrotic inflamed decidua." The nature of this case was not so difficult to recognize because of the double vagina and cervix. Later on there will be described a patient in whom there was a single vagina and single cervix and an incomplete abortion from one of two horns. Laparotomy was performed for a suspected ectopic pregnancy.

II. *Uterus bicornis unicollis* is a malformation due to abnormal juxtaposition of Muller's ducts in which the body of the uterus is double but the cervix is fused into one and the vagina is single. In some cases the two uterine bodies may not be widely separated but be in close approximation so that the fundus is bifid and has a saddle shape. *Uterus bicornis unicollis* is found in the dog.

Twelve patients with this anomaly were studied. Since there is a single vagina and single cervix, the diagnosis of some of these cases is sometimes missed and one horn is thought to be the uterus and the other horn an ovarian cyst, a fibroid, or even an ectopic gestation. Anomalies in these cases are occasionally discovered for the first time at operation when two uteri are sounded and curetted or at

laparotomy. Hysterography has also disclosed for the first time in some patients bicornuate uteri. In two cases a small vertical vaginal septum was found extending into the posterior fornix. This suggested the chance for two uterine bodies to be present.

The obstetrical record is a little better than in the previous group. Seven patients conceived. Only one woman was a sterility problem. One conceived four times and miscarried twice. One delivered four full term babies, another two. One patient carried to term once and miscarried once. Two patients miscarried each of their only two pregnancies. One terminated her only pregnancy by induced abortion. Dysmenorrhea was an infrequent complaint in this group and even then was mild when compared to the patients with completely doubled uteri, cervices, and vaginae.

Four cases of uterus bicornis unicollis will be described further.

*Case 1.* The patient was a twenty-five year old woman who had a miscarriage two years previously. She now complained of vaginal bleeding and bearing down pains in the left lower quadrant for one week. There was a history of three skipped periods and symptoms of pregnancy. Because of this and the finding of a mass to the left of and the same size as the uterus, laparotomy was performed for suspected left tubal pregnancy. However, at operation a bicornuate uterus was found; the mass thought to be ectopic was another body of the uterus. There also was present the above described rectovesical ligament; the left tube was enlarged.

A left salpingo-oophorectomy was done. Examination of the tube and ovary showed endometriosis as well as an acute and chronic salpingitis. Later the patient passed tissue identified as necrotic decidua and chorionic villi.

*Case 2.* This patient had a myomectomy done because of a fibromyoma five centimeters in diameter present on the anterior aspect of each uterine horn in exactly corresponding positions.

The third and fourth cases are of interest because of the associated congenital anomalies. One was a thirty-five year old woman with two easily palpable uterine horns entering a single cervix. There was present an infantile vulva with hypoplastic labia majora, minora, and clitoris. Intravenous pyelography demonstrated the presence of a left sacral kidney and a normal right kidney and ureter. By cystoscopy the left ureteral orifice was seen to be pin-point in size. This patient also presented features of a hypothyroid. Menses were normal. She had two spontaneous miscarriages. The fourth case was a sixteen year old girl with two uterine horns, single cervix, absent right kidney and a cyst of Gartner's duct which is a remnant of the Wolffian duct in the embryo.

III. *Uterus arcuatus* is also an anomaly due to faulty juxtaposition of Muller's duct but where the external fundal concavity is the only evidence of bicornuate malformation. Although only two cases are listed, a review of many hystero-grams shows that this condition of bicornuate tendency is common.

IV. *Uterus septus duplex* is a developmental defect due to incomplete absorption of the septum formed by the union of the Mullerian ducts. Externally there appears to be a normal uterus with a convex fundus but there is a septum which passes from the fundus to the cervix so that there are two uterine cavities. When the septum extends only part way down the uterine cavity, the condition is called uterus subseptus. The latter is the normal condition in the horse.

Three cases of this malformation were seen. Interestingly enough two of these

cases had a pyometra, a condition in which purulent material is found in each of the uterine cavities. Hysterectomies were done in each case with *cul de sac* drainage.

The first patient was a fifty-four year old gravida zero and was nine years post-menopausal. For three months she complained of enlargement of the abdomen and a heavy sensation in the pelvis. On examination a large mass was found rising almost to the umbilicus and a smaller mass on the right. At operation a uterus enlarged to the size of a four months gravidity was found. When opened up two uterine cavities were seen, both filled with pus, a double pyometra.

A second patient, presently on the gynecologic ward, had a pyometra in a uterus subseptus containing multiple fibromyomata.

A third patient was discovered to have a septum completely dividing the uterine cavity into two by sounding the two openings in a cervix during a cystorectocele operation. An aperture was searched for by two sounds, but was not found.

It may be mentioned here that in higher degrees of symmetrical malformations of the uterus, such as uterus bicornis duplex, some gynecologists perform a metroplastic operation whereby the separated halves of the uterine horns are united. The indications listed are sterility believed due to the malformation and when several abortions have occurred and are thought to be due to this anomalous development.

V. *Patent septum between two uterine cavities*, resulting in one uterine cavity communicating with the other, existed in two patients both of whom had two cervixes and two vaginae.

The first was a thirty-five year old woman admitted for sterility study. With the cannula in the left cervical canal, radiopaque oil was injected and the x-ray film showed two small uterine cavities and two Fallopian tubes clearly outlined. Later with cannula in right cervical canal, I repeated the procedure and the same hysterosalpingogram was obtained. The second case was similar but was discovered during an operation for excision of the vaginal septum and curettage of both uteri for menometrorrhagia. It was found that the sound in the left cervical canal met the curette in the right side of the uterus. One patient was married for three years, the other for one year and neither had as yet conceived.

VI. *Uterus unicornis* is a condition in which only one Mullerian duct develops, the other aplastic. Thus, the patient has a vagina, uterus, one tube, and one round ligament derived from this duct. The process of aplasia may be bilateral so that there is an absence of tubes, uterus, and vagina. The latter constitute a very interesting group of cases, many of whom have had artificial vaginae constructed surgically. These will be described separately later.

Uterus unicornis was present in a twenty-seven year old woman who was admitted with the complaints of severe dysmenorrhea, menorrhagia, and sterility. Pelvic examination disclosed a normal vagina, small cervix, small uterus, and what seemed to be a lemon-sized mass to the right of the latter. At laparotomy there was found a uterine horn two-thirds normal size, on the right side and connected with the cervix. Attached to the horn was a normal tube and an ovary with a corpus luteum. The left uterine half was represented by a solid fibromuscular mass of tissue, size of a butternut. There was no round ligament, tube, or ovary on this side. The menarche was at the age of fourteen years. Periods occurred every twenty-five to thirty-six days, lasting for six days.

VII. *Hypoplasia or rudimentary development* may be symmetrical, in cases in which both Mullerian ducts give rise to tubes, uterus, and vagina which are solid structures without cavities. Or they may be asymmetrical, so that a uterus

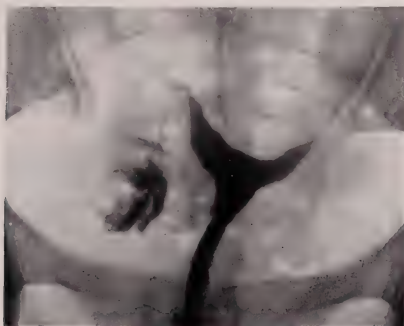


FIG. 1. Hysterosalpingogram showing bicornuate uterus with old right tubal pregnancy. A radiopaque dye is injected with a cannula and syringe into the uterine cavity. The long cannula can be seen in the photograph.

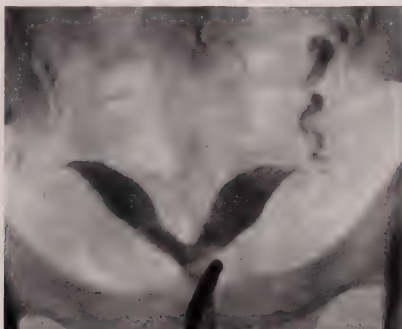


FIG. 2. Uterus bicornis unicollis. This is the hysterosalpingogram of the third case described in the text under this type of malformation. The patient had a hypoplastic vulva, left sacral kidney, and was a hypothyroid. Her only two pregnancies terminated in spontaneous miscarriages. Menses were normal and regular.

bicornis results with one of the horns being rudimentary, the latter being solid or tubelike. Further, there may persist in the adult a small uterus with fetal characteristics.

*Case 1.* This was a fifteen year old girl with a hematometra and hematosalpinx, namely a collection of menstrual blood in a rudimentary tube and uterus which had no communica-



tion with the relatively normal uterus and cervix. The girl had always had regular periods but with severe menstrual cramps the first two days. Twenty-four hours before admission she developed marked cramp-like pains in the right lower quadrant. Intravenous pyelography showed an absent kidney on the right and a kidney with dilated pelvis on the left. The day before admission, two weeks after the last period, severe right lower quadrant pains set in. Examination revealed a fixed tender mass in the right pelvis. A smaller mass was present posteriorly and to the left of the cervix. At operation it was apparent that there was complete failure of fusion of the halves of the Mullerian ducts. On the left was a uterus of normal size with one tube, ovary, and round ligament, all deep in the *cul de sac*. On the right was a huge hematosalpinx, 8 inches long and 2 inches in diameter, adherent to the right ovary which appeared normal. This large tube arose from the right side of a hematometra measuring 6 x 3 x 3 inches. The right uterus and tube were removed.



FIG. 3. Uterus bicornis duplex. Two cannulas are seen inside the two uterine cavities. There are present two vaginæ, two cervixes, and two uteri. The patient's only pregnancy was spontaneously aborted.

*Case 2.* This was a miscarriage from the right, the more normal horn of a uterus bicornis with a rudimentary horn. A 38 year old housewife was admitted for vaginal bleeding and cramps for two weeks following a period of amenorrhea of three months. Two cervixes, completely separated by a partial vaginal septum, were found. The left cervix was small and closed; the right cervix was hypertrophied and patulous. The right uterus was enlarged to the size of an eight weeks gestation. The left uterus was small. By speculum blood could be seen oozing from the right cervical canal. Adnexa could not be palpated. A dilatation and curettage were done; the uterus sounded three inches in depth. Fragments of placental tissue were obtained. In this same uterus she carried two babies to term and had also had one previous spontaneous miscarriage.

*Case 3.* This was a very unusual case of a cervical hematometra, namely a collection of menstrual blood in a sac in the cervix. The patient, a twenty-one year old nulligravida, complained of intermenstrual staining for two years. At pelvic examination there was found a patulous cervix to the right while to the left in the vaginal wall, adjacent to the cervix, was a mass five centimeters in diameter. The uterus was sinistroversed. Hystero-graphy demonstrated that there was a bicornuate uterus, the cavity of the uterus on the right leading into the single cervical canal and the cavity of the left uterus leading first into a dilated sac in the cervix containing blood. Then from the latter sac could be seen

a tiny opening leading into the above cervical canal. Resection of the left horn of the uterus, excision of the cervical hematometra, and anastomosis of the right horn with the remaining cervix were performed. Normal menses ensued.

The above cases illustrate some of the diagnostic and surgical problems presented by such anomalies. Much has been written on the disastrous aspects of pregnancy when an ovum develops in a rudimentary horn of the uterus. A rudimentary horn which has no communication with the uterine canal may become impregnated by a wandering fertilized ovum from the opposite side. This usually ruptures within the first four months into the abdominal cavity with the picture of ruptured tubal or interstitial gestation. Occasionally the fetus dies

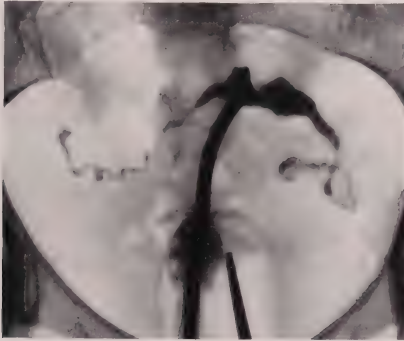


FIG. 4. This demonstrates a double uterus with a patent septum so that the two uterine cavities communicate with each other. The same picture was seen when the radiopaque dye was injected into the left cervical canal and later into the right cervical canal. Two distinct cervixes and two vaginae were present. Case described in text.

within the rudimentary horn without the occurrence of rupture. Even the more normal horn of the uterus may rupture because of the defective musculature. There may be weak uterine contractions in labor, breech and transverse presentations occur with greater frequency, and the non-pregnant uterus may become incarcerated under the pregnant portion, causing dystocia and rupture of the uterus. A septum present in the cervix may prove to be an obstruction to the delivery of the child. Two cases have been described where the child straddled the septum. Finally, post-partum hemorrhage may occur from an atonic uterus or from the septum in the uterus when it is the site of placental attachment or is lacerated in delivery.

#### SUMMARY

Thirty-five cases of congenital malformations of the uterus, tubes, and vagina are presented.

It is seen that sterility, spontaneous miscarriages, and dysmenorrhea are prominent features of such cases.

Some of the diagnostic and surgical aspects are discussed.

A number of the obstetrical dangers are outlined.

A clinical picture at times almost indistinguishable from tubal pregnancy may be presented by a threatened miscarriage in one of two horns of a bicornuate uterus.

Cases of double pyometra, cervical hematometra, and hematometra with hematosalpinx are described.

Hysterosalpingography is making the discovery of anomalies more frequent and is of considerable value in determining the exact anatomical variation being studied.

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## TEMPORARY FUNCTIONAL INHIBITION OF THE KIDNEY ITS CLINICAL SIGNIFICANCE

MOSES SWICK, M.D.

(*New York, N. Y.*)

In my original articles on intravenous pyelography, I touched upon the subject of temporary functional inhibition of the kidney in a discussion of renal function as it pertains to intravenous urography. Yet, during a recent presentation and discussion, I found that that relationship was not clearly appreciated, nor the concept and importance of temporary renal functional inhibition recognized. It is for this reason that I am presenting the following general considerations with particular emphasis upon the question of temporary renal functional inhibition as demonstrated by two case illustrations.

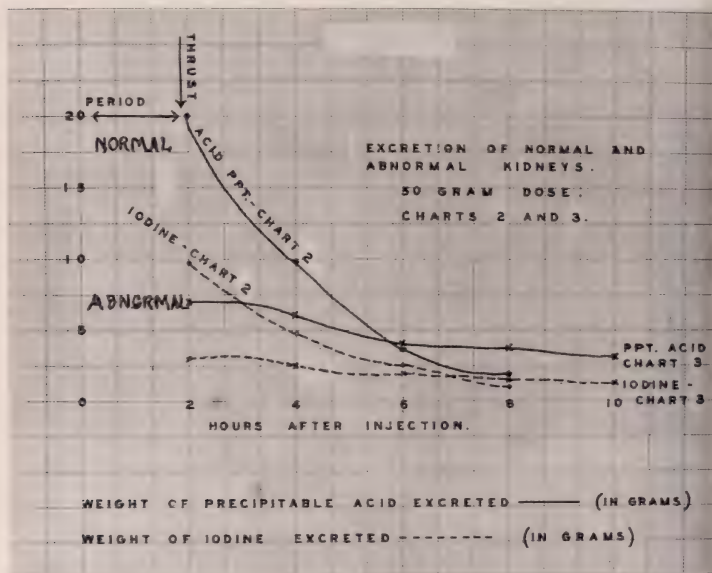
The success of intravenous urography rests upon the functional activity of the renal parenchyma, namely, the concentrating power. The normally functioning kidney possesses the ability to excrete urographic substances in high concentration in a given short period—this may be characterized as the “thrust excretion ability of the normally functioning kidney.” Thus, about 70 to 80 per cent of the urographic medium is excreted during the first two hours after the intravenous administration of the dye (table I). As a corollary, when this concentrating power is either impaired or absent, as in the poorly functioning kidney, the roentgenologic visualization is correspondingly poor or entirely absent. Broadly speaking then, the degree of visualization, other things being equal, depends upon renal and extrarenal factors determining renal excretion. However, in the presence of urinary tract obstruction, visualization may still be observed despite the fact that the normal level of excretion ordinarily required for roentgenologic purposes is below the threshold, provided that excretion still exists. Thus, in obstructive uropathic reservoir-like mechanisms, such as hydronephrosis, under which circumstances small amounts of excreted dye may progressively accumulate, dense visualization may still be encountered in spite of the existence of relatively little intact renal tissue.

Now, concerning the point in question, the functional activity of the kidney may be temporarily diminished or totally inhibited as a result of severe trauma, or acutely occluding lesions of the urinary tract although the kidney parenchyma itself may be intact. The concept—temporary functional inhibition—is employed advisedly when non-visualization of a urinary tract at one examination has been followed by the restoration of function and visualization with the removal of the causative factor. I will not attempt here to enter into a discussion of the mechanism involved, be it on the basis of neurogenic influences upon the vascular tree and the cellular activity of the kidney, or, upon hydrostatic factors such as increased intrarenal pressure with its influence on glomerular filtration and tubular excretion of the urographic medium. An explanation of the mechanism of temporary functional inhibition may now perhaps be gained from the

experimental work reported by Trueta and his associates. In his report on renal pathology in the light of neurovascular studies, he states that with appropriate nerve stimulation in animals, the renal blood flow may be diverted from its commonly accepted course with the result that the cortex of the kidney may be partly or wholly deprived of its blood supply. Thus by a short-circuiting of the blood supply through a lesser circulation of the kidney by way of the *vasa recta*,

TABLE I

*Chart of curves of excretion of a normally functioning, and of an abnormally poorly functioning kidney*



their loops and the subcortical plexus of vessels, the cortex is made functionally ischemic. Simultaneously the flow of urine through the ureter has been observed to be decreased or entirely suppressed. Trueta's work demonstrates the importance of the mechanism by which a temporary or permanent cortical ischemia may be produced without arrest of the renal circulation. This mechanism perhaps may explain the *modus operandi* of the cases to be presented. Suffice it to state that such a situation may exist as exemplified by the following two case illustrations. Furthermore, it will be observed from these illustrations that the mere non-visualization at a given examination does not necessarily denote



permanent irreparable renal damage. I wish to stress this point, since in the past, kidneys have erroneously been sacrificed because of a lack of realization of the above concept.

#### ILLUSTRATIVE CASES

*Case 1.* Cystoscopic examination of a 41 year old man admitted for bilateral lumbar pain revealed *normal indigo carmine* excretion from *both kidneys*. A left retrograde pyelo-



FIG. 1. Non-visualization of the left upper urinary tract and opacification of the left kidney outline following trauma from a left retrograde pyelogram. Visualization of a normally functioning right kidney outlining a double pelvis and forked ureter—temporary functional inhibition (see Figure 2). This intravenous pyelogram was done one week after left retrograde pyelography.

gram simultaneously performed with 12 per cent sodium iodide solution demonstrated a normal left pelvis and calyces. Following this examination, hematuria and severe pain in the left loin set in and persisted for about one week. When both symptoms had subsided, intravenous urography was done. *Absence of visualization of the left upper urinary tract* with opacification of the renal outline were noted; the opposite right side revealed normal function and the presence of a double pelvis and forked ureter (fig. 1). However, another check-up intravenous urogram 3 months later, showed *return of function* and the *visualization of a normal upper urinary tract* on the previously instrumentally pyelogrammed left kidney, together with the above noted findings on the right side (fig. 2)—in other words, a case of temporary functional inhibition of the left kidney following trauma from a retrograde pyelogram. This case also presents the impressive picture of a temporary renal shut-down of at least one week's duration, and illustrates the possible dangers inherent in bilateral retrograde pyelography at one examination particularly with the use of the older inorganic halogens.

*Case 2.* A 42 year old man, one year ago, had had several attacks of right lumbar pain radiating down to the testicle; there were red blood cells in the urine. He supposedly passed a calculus at that time. A urologic check-up four years previously revealed a right non-rotated kidney with some dilatation of the pelvis and calyces, *good function* and clear urine. No calculus was observed then. The present history is of one week's duration starting with pain in the right sacro-iliac region and right lower quadrant of the abdomen,



FIG. 2. Same case as Figure 1 (check-up intravenous pyelogram) depicting return of function of left kidney and outline of a normally appearing upper urinary tract in the previously traumatized pyelogrammed left kidney—three months later.

discomfort in the right testicle, urgency, and frequency of urination. An intravenous pyelogram done elsewhere revealed *no visualization of the right upper urinary tract and a normal arogram on the left side* (fig. 3). At that time right retrograde pyelography was performed, again outlining the same degree of dilatation of the pelvis and calyces of the non-rotated right kidney noted in 1941. The urologist stated that there was *no indigo carmine excretion, no obstruction* encountered to the ureteral catheter, and 8 cc. of clear urine obtained as retention from that side. Following retrograde pyelography, the patient developed a high temperature, chill, pain in the right flank and a rather cloudy urine. Physical examination when seen by me three days later was essentially negative. The urine, however, contained a faint trace of albumin, 20-30 white blood cells and an occasional clump of pus cells per high power field. After his symptoms had subsided, a check-up in-

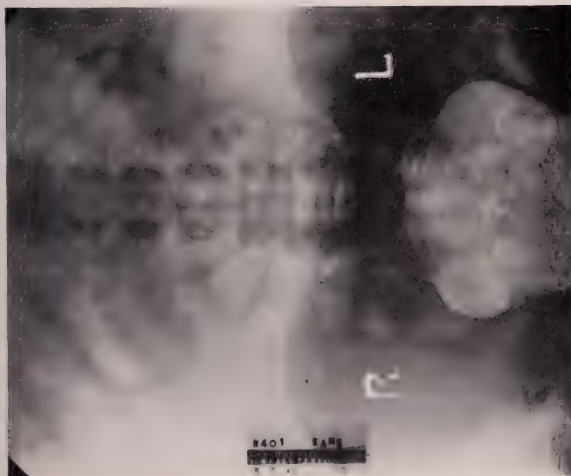


FIG. 3. Intravenous pyelogram depicting nonvisualization of the right upper urinary tract. Left upper urinary tract is normal. This is a case of temporary functional inhibition incidental to a strongly suggestive ureteral calculus (see Figure 4).

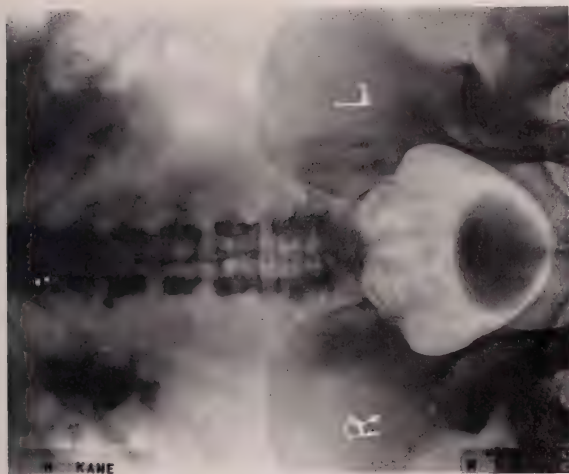


FIG. 4. Check-up intravenous urography, two weeks later revealing return of function of right kidney and the visualization of a nonrotated dilated pelvis and calyces.

travenous pyelogram, two weeks after the above intravenous pyelographic examination, revealed *return of function of the right kidney* as evidenced by the roentgenologic visualization of the above described dilated pelvis and calyces; the left upper urinary tract again appeared normal (fig. 4). No radiopaque urinary calcific shadow was demonstrable. Additional interesting clinical data in this case are the following: the bladder urine revealed a *B. pyocyaneus* infection for which he was treated with 5 grams of streptomycin. Upon this therapy the urine became crystal clear and negative on microscopic examination, but the culture showed a persistent *B. pyocyaneus*. This status remained for about six weeks when his urine again became cloudy and loaded with pus cells, although he remained asymptomatic. The prostatic smear too showed a moderate number of pus cells. Another intravenous pyelographic check-up two months later again revealed good function on both sides and no progression of the dilatation of the right non-rotated kidney. Cystoscopy and ureteral catheterization showed *good indigo carmine* excretion from both kidneys; there was no obstruction to the catheter passed to the right kidney; the urine from the right kidney showed 30-40 white blood cells with some clumps, and a *B. pyocyaneus* on culture from the right kidney and bladder specimens. No radiopaque urinary calcific shadow was found. Eight grams of streptomycin were now administered with the result that the urine became entirely negative both on microscopic and bacteriologic study. The patient has remained asymptomatic and with a completely negative urine for at least a three months' follow-up period. This case also is one of temporary functional inhibition, due, in my opinion, to an obstructing calculus which presumably had passed, with resultant restoration of function and visualization of a dilated pelvis and calyces of a right non-rotated kidney.

#### CONCLUSIONS

Two cases are presented demonstrating the fact that the function of the kidney may be temporarily inhibited, and that the mere non-visualization of a urinary tract at one examination does not necessarily signify permanent irreparable renal damage. Moreover, it is essential to bear in mind that the method of intravenous urography is dependent upon renal and extrarenal factors which influence the concentrating power of the kidney and thus, its function.

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## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Acute Poliomyelitis and Acute Infectious Lymphocytosis—Their Apparent Simultaneous Occurrence in a Summer Camp.* J. S. BELOFF AND K. M. GANG. J. Pediat., 26: 586, June, 1945.

This report deals with an unusual group of cases related in time and space and possibly in etiology. Within a period of 14 days, four children, closely associated at a Camp, developed suggestively related illnesses. The first child sustained a fatal case of bulbar poliomyelitis. The second patient became ill one week later with a clinical picture resembling acute infectious lymphocytosis, the disease entity described by Carl Smith. However, were it not for the white blood cell count of 50,000 with 90 per cent normal lymphocytes, the diagnosis of nonparalytic poliomyelitis could have been made. At approximately the same time another camper developed a clinical picture similar to this latter one with respect to the unusual blood count, and with associated manifestations of multiple paralyses typical of poliomyelitis. The fourth patient had all of the clinical and laboratory criteria of acute nonparalytic poliomyelitis except for definite tenderness of the parotid glands which suggested the possibility of a mumps meningoencephalitis. The differential diagnosis of these cases included acute poliomyelitis, lymphocytic choriomeningitis, mumps meningoencephalitis, tuberculous meningitis, infectious mononucleosis, and acute infectious lymphocytosis. The laboratory data most strongly suggested the presence of acute poliomyelitis and acute infectious lymphocytosis as coexisting entities in these four cases. From the laboratory data and clinical course, two of the children had poliomyelitis whereas the other patients apparently represented unusual examples of acute infectious lymphocytosis. A review of the subject of infectious lymphocytosis with its differential diagnosis is presented. The possible significance of the association in one epidemic area of poliomyelitis and acute infectious lymphocytosis is discussed. It is suggested that infectious lymphocytosis might possibly represent an atypical clinical form of poliomyelitis on the basis of different strains of the poliomyelitis virus.

*Intestinal Injury and Fecal Fistula in Gynecological Surgery.* H. C. FALK AND S. HOCHMAN. Am. J. Surg., 70: 176, June, 1945.

In a series of 5,055 laparotomies performed at Harlem Hospital on the Gynecological Service, there were 42 cases of intestinal injury, of which 18 developed fecal fistulas and 2, generalized peritonitis. The chief predisposing causes of intestinal injury are adhesions and friability of the intestinal wall in pelvic inflammatory disease. The most reliable index of acuteness of pelvic inflammatory disease is the sedimentation rate. A slow rate is the chief prophylactic measure against intestinal injury. Where there is a possibility of intestinal injury, diligent examination of the intestine should be made since recognition and immediate repair is essential. The value of drainage is questionable. In 17 cases there must have been bowel injury which was not recognized at the time of surgery. Fistulas of the sigmoid, rectum and ileum, portions of intestine generally involved in gynecological surgery, usually heal spontaneously within a year.



*Postoperative Vesico-Uterine Fistula*, R. T. FRANK. *Am. J. Obst. & Gynec.*, 49:776, June, 1945.

Following a Manchester operation for prolapse, the first day postoperative, complete leakage of urine was noted from the vagina. This patient was first seen by me five months postoperative. The repair of the prolapse was excellent. A steady stream of urine oozed from the external os. At operation the uterus was found fixed in the pelvis. For an adequate approach, a deep left Schuchardt incision was made. A small tunnel was made by sharp dissection between bladder and amputated cervix reaching almost to the fundus of the uterus. An additional hole was accidentally made in the bladder. The fistula was found high on the corpus and so inaccessible that it could be freed only by excising a button shaped area from the uterus. With great difficulty this portion of the fistula was inverted into the bladder and a single suture for bladder closure inserted. The fresh opening in the bladder was closed in layers and the Schuchardt repaired. Convalescence was uneventful and the patient cured.

*Further Experiences with the Surgical Treatment of Intractable Ulcerative Colitis*. J. H. GARLOCK. *New York State Med. J.*, 45: 1309, June, 1945.

Surgical treatment in intractable ulcerative colitis is indicated in the presence of 1. uncontrollable bowel hemorrhage, 2. acute ulcerative colitis with profound toxemia not responding to sulfonamides or other medical therapy, 3. impending perforation of the colon, 4. chronic intractable colitis with extensive scarring of the bowel, polypoid degeneration or rectovaginal fistulae, resisting all forms of medical therapy and 5. segmental ulcerative colitis. It is the author's conviction that ileostomy is indicated as the initial procedure where there is uncontrollable hemorrhage, acute ulcerative colitis with profound toxemia, impending perforation or intractable colitis involving the entire colon and rectum. The marked improvement of patients following ileostomy is stressed, with marked gain of weight, disappearance of anemia, abatement of toxic symptoms and improvement in appetite. If the disease is confined to the left colon and rectum and the operation is deemed advisable, transverse colostomy instead of ileostomy may be carried out. If the rectum and lower sigmoid are free of disease, the initial operation of choice is an ileosigmoidostomy or ileoproctostomy with division of the terminal ileum and transection of the colon proximal to the anastomosis.

*What is pH? An Explanation of the Various Measures of Acidity Employed in Gastroenterology*. F. HOLLANDER. *Gastroenterology*, 4:497, June, 1945.

Various measures of acidity are at present being used by clinical and experimental workers in gastroenterology, viz. 1. milligrams per cent, 2. degrees of acidity, or chemical units, 3. "normal" concentration and 4. pH units. In the paper all four of the systems of representation are discussed in simple terms. In particular, the pH system is explained in simple arithmetic. The advantages of pH notation are manifold and the author cites the fact that it affords a way of representing and measuring acidity values which are so small that they cannot be determined by titration methods, but which are nevertheless very important physiologically. Secondly, many physiological phenomena vary with the acidity, but the relationship can be explained more simply in terms of any of the other systems of notation. Thirdly, other concentration values besides that of hydrogen can be expressed by a similar type of unit, and finally, the pH notation has given us a convenient way of representing the minute numbers which describe acidities and alkalinities within the physiological range.

*A Modified Sling Operation for Correction of Ptosis*. J. LAVAL. *Arch. Ophthalm.*, 33: 482, June, 1945.

It is recommended that in cases of ptosis where there is no levator action and also paralysis of the superior rectus muscle that a modification of the Reese procedure be used. This is a very simple operation and consists of freeing a strip of orbicularis muscle which is cut

in half at the center. Two tunnels are then made under the skin of the lid up to the periosteum and frontalis muscle above the brow. The strips of orbicularis are pulled through the tunnels and sutured to the periosteum and frontalis. In this way the lid is kept elevated.

*The Problem of Nonfluorescent Ringworm of the Scalp.* O. L. LEVIN AND H. T. BEHRMAN. J. A. M. A., 128: 350, June, 1945.

The authors emphasize that not all fungous infections of the scalp impart a noticeable fluorescence to the diseased hairs. They suggest that all patients suspected of ringworm of the scalp should be carefully studied before the diagnosis is discarded. A negative examination under Wood's light is not sufficient to exclude these cases. In every instance of clinically suspected infection the performance of microscopic and cultural examinations is essential. It is their opinion that the public health aspect of this problem is of extreme importance and must not be overlooked. These children should be reported to the local health authorities in order to insure adequate case finding and supervision of therapy. They should not be permitted to attend school or enter into close contact with other children.

*Is Dermatophytosis a Significant Occupational Health Problem?* S. PECK AND L. SCHWARTZ. Am. J. Pub. Health, 35: 6, June, 1945.

There is very little if any published data which can be used to evaluate the importance of dermatophytosis as a factor in sickness absenteeism among industrial workers. The paper takes up a number of questions. It was found that dermatophytosis was not an important cause of lost time in industry. The most common pathogenic fungus found as the cause of dermatophytosis was trichophyton gypseum. Among several thousand cases examined, there were only ten cases of actual dermatophytosis that required treatment severe enough to lose time from work. There is a common error made in diagnosing ordinary cases of hyperhidrosis with maceration of the skin as fungus infections. It was found that shower room floorings were not very important as foci for dermatophytosis of the feet. The discussion of the differential diagnosis of occupational dermatoses of the hands and dermatophytid is given.

*A Demonstration Model for Uterotubal Insufflation.* I. C. RUBIN. Am. J. Obst. & Gynec., 49: 786, June, 1945.

The author describes a portable durable working model to demonstrate the method of uterotubal insufflation. The model consists of 3 major parts constructed of plastic materials; a translucent posterior section cast in cellulose acetate, representing the abdominal viscera in natural size; an anterior section of plexiglas duplicating the peritoneal cavity and consisting of a double-walled water jacket the inferior portion of which is expanded to contain representations of uterus, tubes and ovaries cast in cellulose acetate; and a lower section carved out of lucite representing vulva and vagina and permitting the introduction of a small speculum. A metal uterine cannula is cemented into the cervical canal which communicates with the fallopian tubes through a hollow uterine cavity. Water introduced into the water jacket acts as a medium through which CO<sub>2</sub> is percolated. To operate the demonstration model the reduction valve of the insufflated apparatus is set at 15 pounds pressure, the speed regulating valve is gauged to the lever 60 cc. per minute and the inflow glass stopcock and the metal stopcock connecting the uterine cannula are opened. Bubbles of CO<sub>2</sub> passed from the fimbriated ends into the water filling the water jacket and, as the model is tilted at an angle of 45 degrees, rise toward the diaphragm when they collect in a manner simulating a subphrenic pneumoperitoneum. By varying the caliber of the rubber tubing with the aid of a screw-clamp, the different graphs characteristic of tubal patency, nonpatency, spasm and partial patency may be reproduced.

The editor of the American Journal of Obstetrics and Gynecology, in which this article appeared, notes that the year 1945 marks the 25th anniversary of the employment of tubal insufflation for diagnostic purposes. The first trial was made in the Mount Sinai Hospital

and the first report based on 55 cases was made in 1920. In 1921 Dawson Furniss applied the name of the originator to the procedure which is now widely known as the Rubin Test. The editor further states that "modification and improvement, with combination of kymographic tracing and other features have marked the progress in this field of an outstanding contribution to American gynecologic practice".

*History of Medicine on Postage Stamps.* H. M. SALZMANN. Stamps, 51: 10, June, 1945.

Physicians and scientists who have helped to build the fundamentals of medicine have been honored on postage stamps, most of them in excellent portraits. From Imhotep of ancient Egypt to Boerhaave and his pupils, the important Viennese School to the great doctors of yesterday like Long, Koch, and Reed are depicted on stamps. Famous anatomists and physiologists like Leonardo, Von Haller, Cajal, Purkinje, Claude Bernard, the great pioneers in science Darwin, Gregor Mendel, Roentgen, the Curies and even laymen like Ling and Braille are in our album. Doctors famous in other fields than medicine appear in our gallery, Sun Yat-sen, Schopenhauer, Clemenceau, Dr. Zamenhof, the inventor of Esperanto. The little postage stamp carried the glory of our profession around the globe.

*Treatment of Acute and Chronic Infections of the Jaws with Antibiotics.* L. STERN. New York J. Dent., 12: 225, June, 1945.

Topical application of penicillin appears to be of limited value in the treatment of ulcerative lesions in and about the mouth. One of the drawbacks is that the agent is dissipated quickly in the mouth and improved results may reward a technic which maintains the penicillin in contact with the lesion for longer periods. Intramuscular injection of moderate doses of penicillin probably widens the margin of safety in the treatment of acute infections of the jaws and brings them under earlier control. Recent experiments indicate that with larger doses of the order of 100,000 units every 3 hours, are well tolerated and far more effective. Nevertheless, the need for surgical treatment is not always eliminated; indeed, residual infection may be marked and exacerbate later. Few, but large doses of penicillin injected close to the infection appear in some cases to be as effective as more frequent intramuscular injections. This method seems to be decisive in the treatment of pericoronitis but it is experimental and not without risk. Many additional data must be accumulated before the indications, limitations and possible extensions of penicillin therapy may be gauged accurately, but enough evidence already exists that it is destined to be an invaluable adjunct in the management of many varieties of infections of the jaws.

*Parinaud's Oculoglandular Syndrome Due to a Yeast-like Organism.* F. H. THEODORE. Arch. Oph., 33: 471, June, 1945.

Parinaud's oculoglandular syndrome is a chronic unioocular granulomatous conjunctivitis with marked regional lymphadenopathy. The most common cause appears to be a leptothrix infection. Other etiologic agents reported include tularemia, tuberculosis, lymphogranuloma venereum, and syphilis. A case is reported which was unique in that, while the ocular condition cleared in a few weeks, regional glandular suppuration occurred, requiring surgical drainage, and ultimate healing was prolonged. Both biopsy material from the involved conjunctiva and smears of pus aspirated from the preauricular gland revealed an organism resembling a yeast. In view of the clinical course and the laboratory findings, it is believed that this yeast-like organism was responsible for the disease.

*Subacute Bacterial Endocarditis in the Aged.* F. D. ZEMAN. Am. Heart J., 29: 661, June, 1945.

At the present time subacute bacterial endocarditis occurs in the aged more frequently than is generally realized. With the increase in the number of old people in the population, an increased incidence of this disease may be expected in the higher age groups. Clinical recognition of subacute bacterial endocarditis depends upon the physician's constant effort to achieve diagnostic accuracy in the aged by utilizing for them the same careful observa-

tion and the same methods of precision commonly employed for the young. The chief obstacle to diagnostic exactitude lies in the multiplicity of the pathologic processes in old people and in the difficulty of determining the relationship of these processes to the total clinical picture. In spite of close observation and study there will still remain a group of cases in which the subacute bacterial endocarditis will first be disclosed on the autopsy table. Additional clinical and pathologic investigations are needed to keep down the number of these post-mortem surprises.

*The Accuracy of Clinical Urinometer.* H. AARON. *Am. J. Clin. Path.*, 15: 7, July 1945.

Standardization of urinometers in use at hospital and private offices disclosed that at least 50 per cent of them were not accurate. In addition many urinometers are not suitably constructed for accurate testing of specific gravity of the urine. Until urinometers are manufactured and standardized in conformity with standards set by a Federal testing agency, physicians should standardize their own urinometers with solutions of known specific gravity.

*Congenital Deafness and Cataract Following Rubella in the Mother.* F. ALTMANN AND A. DINGMANN. *Arch. Otolaryng.* 42: 51, July, 1945.

When a woman contracts rubella during the first two months of pregnancy the chances of her giving birth to a congenitally defective child are 100 per cent. If she contracts the disease in the third month, the chances fall off to 50 per cent. If the disease occurs after the third month, there is only a slight likelihood that the child will be congenitally defective. The most frequent anomalies are congenital cataract, cardiac lesions and deaf-mutism. In the case of the authors a unilateral cataract was combined with deaf-mutism, a combination which hitherto has not been observed. No reaction to sounds could be elicited, but the vestibular response was normal. The mother had contracted German Measles during the later part of the second month of pregnancy.

*Intraperitoneal Nabothian Cyst.* R. T. FRANK. *Am. J. Obst. & Gynec.*, 50: 107, July, 1945.

Laparotomy was performed on a patient, 22 years of age, for the removal of an orange sized simple right ovarian cyst. Before closure, a thin walled cyst was found in the uterine musculature, bulging out into the peritoneal cavity, situated on the posterior uterine wall above the sacrouterine ligaments. The cyst was excised with some uterine wall, the defect repaired. Convalescence was uneventful. Microscopic examination showed that the cyst was a typical, much dilated nabothian follicle which either through congenital displacement of a cervical gland or through some defect in the uterine muscle, had grown backward and upward into the uterine cavity. No such location has previously been noted.

*Glass Syringe For Local Application of Sulfa Powder in Oral Cavity.* D. D. GLUCKSMAN AND M. G. FREID. *Medical Department Bulletin of European Theater*, page 62, July, 1945.

In order to reach the inaccessible places in the mouth, such as deep bone sockets and deep wounds, we used a glass syringe. This syringe is called an Ear and Ulcer syringe. It is glass with a large rubber bulb. Pressure on the bulb caused the powder in the syringe to spray into the area that it was intended for. It made the application of the powder easier, prevented caking.

*Relief of Hypertraumatism of Teeth with an Acrylic Appliance.* D. D. GLUCKSMAN AND M. G. FREID. *Medical Department Bulletin of European Theater*, page 57, July, 1945.

A patient, with a fractured axia and cervical vertebrae, was wearing a head extension collar. He complained of pain in his upper bicuspid teeth. Upon examination, there was no pathology to be found in the oral cavity. There were several teeth missing in the upper jaw. It was decided that the chin piece of the collar was causing the mandible to exert undue pressure on the remaining upper teeth. A removable acrylic appliance was made.



which distributed the trauma over all the remaining teeth and alveolar ridges of the upper jaw. The pain disappeared and the necessary pressure of the head collar was able to be maintained.

*Dermatitis From Dehydration of Potatoes.* S. PECK AND H. C. CLARE. Arch. Dermat. & Syph., 52: 9, July, 1945.

An investigation of the dermatitis seen in the dehydration of vegetables, that is, the dehydration of potatoes, was made. The process of dehydration is described. The clinical investigations were conducted in several plants and 24 women with dermatitis were seen among those exposed. The greatest number of cases were observed in the plant in which lye was used to remove the peel. However, it was found that the dermatitis seen in the process of dehydrating potatoes was due to the long hours of exposure to water and potato juice which results in varying degrees of maceration of the skin. Secondary invasion by cocci or monilia organisms also play a role in the clinical syndromes. Proper protection of the skin by ointments and gloves easily prevented the dermatitis.

*A Needle Holder for Oral Surgery.* R. M. RANKOW. J. Oral Surg., 3: 228, July, 1945.

The teeth, lips and cheeks particularly in the distal areas of the mouth, greatly limit the use of straight-beaked needle holders in suturing the various incisions required in certain oral surgical procedures. A needle holder is presented which is constructed of stainless steel and has the shaft at right angles to the beaks. An angulation of 115 degrees has been given to the nose of the beaks to permit the head of the instrument to clear the protruding alveolar crests when the needle is rotated from the flap to the fixed tissues. This design results in improved visibility and accessibility to the suturing site, which offers economy of operative time and minimal tissue trauma.

*Benign Paroxysmal Peritonitis.* S. SIEGAL. Ann. Int. Med., 23: 1, July, 1945.

Five cases are presented illustrating a syndrome of recurrent paroxysms of severe abdominal pain, with fever usually 101 to 103° but which may reach 105°. A shaking chill may occur. Peritoneal involvement is indicated by widespread, direct and rebound tenderness, often exquisite in degree. Occasionally true involuntary spasm of the abdominal wall is present. The findings are such that the surgeon often diagnoses acute appendicitis, or some other acute peritonitic lesion may be suspected and immediate operation advised. Chest pain of a pleuritic type is frequently present at some stage of the attack. Marked malaise, prostration and nausea and vomiting are usual accompaniments. Leukocytosis and polynucleosis are often present. Diarrhea is usually absent. In one case a few urticarial wheals appeared with many of the episodes. The average duration of the paroxysms is two to three days and the free interval varies from one week to four or even six months. This disease affects young people, often beginning in the second or third decade of life and continuing for many years. The average duration of the disease in this series has been 14 years, the longest case being 25 years. Nevertheless the general condition of these patients remains excellent and there is never any evidence of the development of any persistent anatomic lesion. In one instance abdominal exploration during the acute attack revealed injection of subserosal blood vessels involving both small and large bowel lying in the lower abdomen. This finding, together with the clinical characteristics of the disease, indicates that the essential lesion is a readily reversible one, consisting of vascular dilatation and hyper-permeability. Apparently its localization is chiefly in the peritoneum although there is evidence to suggest involvement of the pleura and possibly the synovia as well. The conception of this disease as separable from the larger category of Osler's erythema and Henoch's purpura is discussed. Its probable relation to the allergic state is considerable in detail. Suggestions are offered as to diagnosis and treatment.

*Clinical and Electroencephalographic Studies of Changes of Cerebral Function Associated with Variations in the Blood Sugar.* H. STRAUSS AND I. S. WECHSLER. Am. J. Psychiat., 102: 34, July, 1945.



A group of psychoneurotics is described showing an unusual lability of the electroencephalogram to hyperventilation in the presence of normal blood sugar levels and a disappearance of this lability when the blood sugar is increased further. The relationship between the presence of nervous complaints in the early morning and the development of delta activity on hyperventilation in the fasting state was studied. Delta activity develops more frequently in subjects having such complaints than in subjects without them. Subjects developing delta activity on hyperventilation in the fasting state feel, in a larger percentage, better at later hours than patients without delta activity. Two cases of spontaneous hypoglycemia with electroencephalographic studies are reported.

*The Influence of Dietary Deficiencies and Various Poisons on the Histochemical Distribution of Phosphatase in the Liver.* M. WACHSTEIN. Arch. Path., 40: 57, July, 1945.

In the livers of normal rats, mice and rabbits, alkaline and acid phosphatase are regularly found in the chromatin substance of the nuclei. Acid phosphatase is present in the cytoplasm of liver cells in much larger amount than alkaline phosphatase. Increase in cytoplasmic alkaline phosphatase activity is seen in the atrophic liver cells of starved, and in the hydropic liver cells of protein-depleted mice, and to a lesser degree in those of rats. Adenomatous fat-free areas of cirrhotic livers are often the seat of marked alkaline phosphatase activity. In the necrotic liver cells of animals poisoned by phosphorus, chloroform and carbon tetrachloride, no or only very slight increase in enzymatic activity was found. The increase in alkaline phosphatase activity observed in starvation and protein depletion suggests the intensification of metabolic processes dependent on the action of this enzyme. Since little change occurs in necrosis of liver cells, it is assumed that the damaged liver itself does not contribute materially to the increased amount of alkaline serum phosphatase observed in different forms of hepatic disease.

*The Lability of Ocular Tension. A Test to Determine Individual Variations.* S. BLOOMFIELD AND R. K. LAMBERT. Arch. Ophth., 34: 83, August, 1945.

The maintenance of intraocular pressure within a normal range suggests the presence of a regulatory mechanism. Dysfunction of such a homeostatic system may result in an abnormal lability of intraocular pressure and may eventuate into simple glaucoma. The method described to test this lability may prove of value for the earlier diagnosis of chronic simple glaucoma and the evaluation of therapeutic measures for that disease.

*A Comparison of Several Preparations of Protamine Zinc Insulin in the Treatment of Diabetes Mellitus.* H. DOLGER. Bull. New York Acad. Med., 21: 436, August, 1945.

Twenty-five patients with severe diabetes mellitus who had been treated with extemporaneous mixtures of insulin and protamine zinc insulin were subject for the trial of three modifications of protamine zinc insulin. Two of these were acid and therefore clear solutions, the third was neutral and cloudy, containing only one-third the amount of protamine present in the commercial type. The acid preparations were unsatisfactory in that like globin insulin they caused afternoon hypoglycemia and failed to cover nocturnal glycosuria. The neutral preparation was ideal in controlling glycosuria and freedom from shocks to a degree resembling mixtures of two parts regular to one part protamine zinc insulin.

*Heminecrosis of Cervical Stump Following Supravaginal Hysterectomy.* R. T. FRANK. Am. J. Obst. & Gynec., 50: 226 August, 1945.

A typical supravaginal hysterectomy for multiple fibroids was performed on a thirty-nine year old nullipara. The convalescence was afebrile until the tenth day. On the eleventh day there was profuse vaginal bleeding, temperature 103.6 degrees, a white blood count 19,000 but no peritoneal symptoms. On pelvic examination, the right side of the portio vaginalis was found enlarged due to a sharply demarcated necrosis of one-half of the cervix. The necrosis extended into the vaginal fornix. Three days later the entire necrotic area was removed as a slough. From then on the convalescence was uninterrupted. Presum-

ably the descending vaginal vessels on the right were anomalous and without free anastomosis with the ascending vaginal vessels. Consequent ischemic necrosis occurred.

*Traumatic Right Diaphragmatic Hernia.* L. H. KEENE AND B. COPLEMAN. *Ann. Surg.*, 122: 191, August, 1945.

A case is described in which the right hemidiaphragm was detached through approximately 70 per cent of its costal origin. About 4 weeks after the original injury the liver herniated into the chest, rotating 180° on its long axis as it did so. Roentgenographic studies, particularly those of the gall bladder suggested the disordered anatomy which was found at the operation.

*Which Kind of Irregularity Should be Called a Trigeminus?* B. KISCH. *Exper. Med. & Surg.*, 3: 191, August, 1945.

Out of historical as well as logical reasons, a Trigeminus or Quadrigeminus respectively, should only be designated as a condition in which each normal beat for a more or less long period of time is followed in a fixed distance by two or three extra systoles respectively.

*Strain of the Pectoralis Minor Muscle, an Important Cause of Precordial Pain in Soldiers.* M. MENDLOWITZ. *Am. Heart J.*, 30: 123, August, 1945.

Pectoralis minor muscle strain is a hitherto undescribed cause of anterior chest pain common in soldiers. It is characterized by pain in the right or left anterior chest usually radiating to the corresponding shoulder, often aggravated by deep inspiration and associated with tenderness at the level of the third, fourth or fifth ribs in the mid-clavicular line. Bringing the upper arm from a dorsal position forward against resistance reproduces or intensifies the pain and procaine injection at the site of maximal tenderness causes the pain to disappear.

*The Surgical Significance of an Anomalous Cholecystohepatic Duct.* H. NEUHOF AND S. BLOOMFIELD. *Ann. Surg.* 122: 2, August, 1945.

The existence and surgical significance of an anomalous duct between liver and gall-bladder (to which is attached the term "cholecystohepatic" duct) can be understood best by a consideration of its embryology. Although a duct of substantial proportions probably is a rare anomaly, its presence at the operation of cholecystectomy creates an important problem. Since the duct is inevitably severed during cholecystectomy, its nonrecognition, because of uncontrolled leakage of bile, may lead to peritonitis, localized infection, or the symptoms of prolonged biliary deprivation. Ligation of the duct is probably a safe procedure in most cases. In the presence of stasis and infection within the segment of liver drained by the duct, drainage and not ligation may be indicated despite the complications which are invited.

*Late Invasion of the Bladder and Prostate by Carcinoma of the Rectum or Sigmoid.* G. D<sup>r</sup> OPPENHEIMER. *J. Urol.*, 54: 162, August, 1945.

Fifteen cases observed and treated at the Mount Sinai Hospital following abdomino-perineal resection for carcinoma of the rectum later showed invasion of the bladder and/or prostate and seminal vesicles. In a series of fifty autopsied cases reviewed at Montefiore Hospital (20 per cent had rectal resection), there was invasion of the bladder in 21 cases. The involvement occurs by direct extension of the neoplasm or, in operated cases, it occurs from residual cancer. Contributing to the death of 61 per cent of these 50 cases, was upper urinary tract complication either by direct invasion of the ureters, or more frequently by low peri-ureteral obstruction with upper tract infection. Metastases, rather than direct extension to the upper or lower urinary tract are rare. The situation would appear hopeless if invasion of the urinary tract occurs after radical extirpation of large bowel malignancy. However, life has been prolonged in several cases by fulguration and resection of the secondary tumor of the bladder and by radiation therapy. Several illustrative cases are cited.

*Dermatitis From Wearing Apparel.* S. PECK AND L. SCHWARTZ. J. A. M. A., 128: 1209, August, 1945.

The authors discuss the causes of dermatitis from wearing apparel. Fabrics including the synthetic fibers as well as glass cloth and the synthetic films are discussed. Dermatitis from rubber is reported and discussed, and the ingredients in the rubber responsible for the dermatitis is given. Also the question of dermatitis from articles of clothing made from synthetic rubber is discussed. The subject of dyes and mordants in wearing apparel as the cause of dermatitis is given in detail. All sorts of finishing materials are described as well as the new field of mildewproofing agents. Tables and lists of the concentration causing dermatitis are given. There are also discussions of the dermatitis from furs, jewelry, etc. The methods of patch testing with the various articles of clothing to try and trace the specific chemical causing the dermatitis are given.

*Occlusion of the Superior Vena Cava Due to Syphilitic Mediastinitis.* F. D. ZEMAN. J. Thoracic Surg., 14: 330, August, 1945.

Occlusion of the superior vena cava in a man, now 68 years old, has been described in its onset and after a nineteen-year interval. The cause of the obstructive symptoms and signs has been explained on the basis of syphilitic mediastinitis with secondary venous thrombosis. The diagnostic value of the measurement of venous pressures in the upper and lower extremities, as well as of the determination of the circulation times, has been emphasized. The vivid localization of the sites of obstruction in the great thoracic veins and the striking visualization of the collateral circulation by venography are evident from the accompanying illustrations. Particularly noteworthy is the delineation of the vena azygos major due to the reversal of the blood flow. From a clinical viewpoint, the presence of transitory edema of the head and neck, observable on arising in the morning and disappearing slowly after assuming the upright position, must be kept in mind as a pathognomonic sign of venous obstruction in the upper mediastinum. Confirmatory signs are to be sought in disturbances of the venous pressure and circulation time in the upper extremities.

*Operative Cure of Inguinal Hernia in Infancy and Childhood.* J. S. COLES. Am. J. Surg., 69: 366, September, 1945.

A follow-up study comprising a period of 6 months to 6 years of 88 cases of indirect inguinal hernia, in which children were treated by simple isolation and ligation of the neck of the sac, is presented. One recurrence, not related to the type of operation performed, and no case of testicular atrophy are demonstrated. The author postulates that all hydroceles in children are associated with or without a hernia apparent upon clinical examination. They are caused by the trapping of fluid distal to a stenosed portion of the processus or tunica vaginalis, after the fluid has migrated from the peritoneal cavity into a patent funicular ligament. Simple ligation of the hernial sac at its neck cured all the hydroceles present in the series.

*Anomalous Right Subclavian Artery.* B. COPLEMAN. Am. J. Roentgenol., 54: 270, September, 1945.

The embryology and anatomy of the anomalous right subclavian artery are described. The literature is reviewed and the roentgenologic diagnosis discussed. A case showing the diagnostic roentgenologic signs is described.

*Neurologic Complications Following Dengue.* A. KAPLAN. U. S. Nav. M. Bull., 45: 506, September, 1945.

During a recent campaign in the Central Pacific 1488 cases of dengue fever were studied and treated within 40 days. About one month after the crest of the epidemic had passed, varied neurological disturbances were observed in several patients. At first these abnormalities were interpreted as due to some obscure cause. Closer investigation, however, showed that they began mostly within a fortnight of dengue fever and were not related to any other

illness, trauma, toxic factors or dietary deficiency. Two patients had peripheral (Bell's) facial nerve palsy; two, palative nerve palsy; two, long thoracic nerve palsy; two, ulnar nerve palsy; four, peroneal nerve palsy and one had sciatic neuritis. Dengue fever is a "one week" disease and fortunately has a low mortality. It is due to a filtrable virus transmitted by the mosquito *aedes aegypti*. As in other virus diseases, the dengue fever virus may have a latent affinity for the nervous system. Still has suggested that there are several strains of dengue fever virus, immunity being variable and individual. Possibly one of these strains may be neurotropic for the peripheral nervous system. It may be argued that vitamin deficiency is the underlying cause for these abnormal neurological manifestations; although the men affected had previously been through a rugged period of combat on C rations, during their illness with dengue fever most were receiving multi-vitamins and had a varied and adequate diet. In some cases the men had been off ships only a few weeks, had not been in combat and had had an abundance of fresh food. Length of duty overseas varied from 4 to 32 months. All the men had received tetanus toxoid four months to one year prior to developing dengue fever. Several had received recent typhoid inoculations.

*Edema with Hypoproteinemia Due to a Congenital Defect in Protein Formation.* B. SCHICK AND J. W. GREENBAUM. J. Pediat., 27: 241, September, 1945.

A case of congenital hypoproteinemia is reported. There appeared to be a defective formation of albumin and globulin, particularly the gamma globulin. There was no susceptibility to infection although some deficiency in the formation of antibodies was noted. As the gamma globulin is accepted to be the main carrier of humoral antibodies it is surprising that the child enjoyed excellent health with no susceptibility to colds or other frequent childhood infections. The only disturbance has been the edema. The child was never absent from school on account of tonsillitis or colds. This suggests the possibility that humoral immunity may not be the only basis for an individual's resistance against infection but that other mechanisms, particularly the cellular immunity, may play a definite role in producing antibodies rapidly. The negative Schick and Dick tests demonstrate the presence of a certain amount of humoral antibodies. A high protein diet, amino acids orally, and antigenic stimulation did not affect the level of the serum protein nor the clinical picture of recurrent edema. There was a suggestion of liver damage in the laboratory studies. There was no change in the clinical picture of recurrent edema during the period of observation from birth to the age of 12 years. The fact that edema may be caused by a disturbance of the liver function suggests that the edema in nephrosis and even other symptoms of nephrosis may be due to liver damage. Whereas the symptoms in our case may have their basis in an insufficient production of normal protein, particularly of gamma globulin, the symptoms of nephrosis may be due not only to the reduction in the manufacture of normal proteins, but also to the production of abnormal protein. In this connection it is interesting to note that according to investigations of Goettsch and Reeves the albumin fraction of plasma in nephrosis is immunologically different from normal protein. Whether normal or abnormal proteins are formed seems to be more important in the pathogenesis of nephrosis and of other forms of edema than the simple loss of protein by the kidney or the lack of sufficient amount of protein in the diet.

*Etiology of Thromboangiitis Obliterans.* S. SILBERT. J. A. M. A 129: 5, September, 1945.

One hundred typical cases of thromboangiitis obliterans who had been restored to good condition by treatment were personally followed from ten to twenty years. All of these patients were smokers and all of them stopped smoking completely at the beginning of treatment and have not resumed since. In all of them, the disease has remained completely arrested following the initial period of treatment. No measures of any kind to combat infection were used in this group of patients. None were prohibited from eating rye bread or using rye whisky nor were there any other restrictions of diet. The use of tobacco is the sole factor constantly associated with the occurrence and progression of thromboangiitis obliterans. The disease is completely arrested by cessation of the use of tobacco. Throm-



boangitis obliterans is caused by smoking in individuals constitutionally sensitive to tobacco.

*Putrid Pulmonary Abscess Without Foul Sputum (Shut-off Pulmonary Abscess).* D. STATS. Arch. Int. Med., 76: 154, September, 1945.

The early appearance of fetid sputum establishes the diagnosis of acute putrid pulmonary abscess in the great preponderance of cases. Foul sputum does not appear at all or makes its appearance much later than usual in about 5 per cent of the cases. The diagnosis should be entertained when (1) a cause for a putrid pulmonary abscess exists (or, in the absence of a cause, dental hygiene is poor); (2) thoracic pain is severe, prolonged or recurrent; (3) cough and expectoration are minimal or absent, and (4) the roentgenogram reveals persistent pulmonary infiltration with or without pleural effusion. There are grave dangers inherent in a too long delayed diagnosis, but there is a likelihood of a correct diagnosis if the possibility of this lesion is borne in mind. The excellent results which can be achieved by adequate operations on the pulmonary abscess as well as on the complicating empyema, which is often present, provide an additional incentive to establishing the diagnosis of shut-off putrid pulmonary abscess.

*Aural Manifestations of Leukemia.* J. G. DRUSS. Arch. Otolaryng., 42: 267, October, 1945.

A study was made of the aural involvement in 148 cases of leukemia admitted to the Mount Sinai Hospital and a more detailed study of 4 of the patients who died and from whom a temporal bone was procured for histologic examination. Aural complications occurred in 25 of the 148 cases reviewed or in 16.8 per cent. This incidence would undoubtedly have been higher if routine examination of the ears including functional tests of the cochlear and vestibular nerves had been made in each case. The aural complications included diseases of the external, the middle and the internal ear and their adnexa. The pathologic changes in the ear, as elsewhere in the body are comprised chiefly of hemorrhage, leukemic infiltration and inflammation. They may be revealed on histologic examination even in these cases in which there was at no time during the illness any clinical evidence of aural disease. Furthermore, otitic infections are comparatively more severe in the leukemic than in the non-leukemic patient; they not infrequently show a strong tendency to early invasion of the adjacent structures. The diagnosis of acute mastoiditis in a leukemic subject may paradoxically be made more difficult by the presence of post-auricular swelling and sagging of the bony external canal, since these signs, so well recognized as pathognomonic of suppuration in the mastoid bone, may under such circumstances also represent leukemic infiltrations in the adjacent soft parts.

*Endolumbar Pneumoencephalography; Simplified. A Note on Its Advantages.* J. H. GLOBUS AND J. L. SIMON. J. Nerv. & Ment. Dis., 102: 412, October, 1945.

The authors point out some disadvantages of the common method of pneumoencephalography, in which the patient is seated on a prepared chair in the hospital X-ray department. They advocate, instead, injecting the air while the patient is still in bed. The authors' method is first to administer a sedative. Then, with the patient on his side, they apply local anesthesia and perform the lumbar puncture. Once the needle is in place, they raise the head of the bed on tall shock blocks or on chairs, and proceed to remove fluid and inject air. The patient is then transferred to the X-ray department where the films are made. This method has yielded satisfactory results. It is safer and more comfortable for the patient, as well as more convenient for the physician.

*Headache from Malaria.* A. KAPLAN. J. A. M. A., 129: 612, October, 1945.

Attention is focused on a type of headache which will present itself with increasing frequency as more of our personnel who served in the Pacific combat areas are demobilized. Malaria is a "great imitator" and will have to be included with greater frequency in the differential diagnosis of many diseases. A negative blood smear or even several negative blood



smears for malaria in a patient who has had or was exposed to malaria does not rule out the existence of the malarial parasite. In over a dozen patients presenting only the symptoms of recurrent headache blood smears repeatedly failed to show the plasmodium parasite. In these patients the administration of quinine sulphate grains 15 or adrenalin, 2 minims subcutaneously, invariably resulted in the appearance of the malarial parasite in the blood stream within 2 to 4 hours after the medication was given. A blood smear taken during this interval clinched the diagnosis.

*The Danger of Continued Arsenotherapy in Cases of Erythema of the Ninth Day.* W. LEIFER. *Am. J. M. Sc.*, 210: 458, October, 1945.

Fourteen cases of characteristic reaction occurring early in the course of arsenotherapy (6 to 11 days after the first injection) are reported. Only 3 of the 14 patients had a concomitant eruption. The relationship of this reaction to "erythema of the 9th day" is discussed. In all 14 patients early continuation of arsenic after the initial reaction led to serious parenchymatous damage, in the form of jaundice, agranulocytosis, with or without nephritis. The case with which the reaction is misinterpreted or minimized is indicated, and the need for careful evaluation of fever in the early phases of arsenotherapy is stressed. Twelve of the 14 patients subsequently received an intensive course of penicillin without untoward reaction.

*Aseptic Necrosis of the Astragalus Following Arthrodesing Procedures of the Tarsus.* F. M. MAREK AND A. J. SCHEIN. *J. Bone & Joint Surg.*, 27: 587, October, 1945.

Aseptic necrosis of the body of the astragalus was found as a sequel and complication following extensive remodelling of the tarsal bones incidental to arthrodesing procedures of the foot. If early weight bearing is allowed in the presence of this, the weakened astragalus will collapse and thus a secondary traumatic arthritis of the ankle joint will be initiated. If however, aseptic necrosis is discovered early following operation, and weight bearing avoided, revascularization will take place fairly promptly without changes in the contours of the bone. Five illustrative cases are cited.

*Psychological Problems in Training 16 and 17 Year Old Youths in the United States Maritime Service.* J. MARMOR AND A. F. ZANDER. *Am. J. Orthopsychiat.*, 15: 571, October, 1945.

Study of 16 and 17 year old recruits at a U. S. Maritime Service training station revealed that a significantly large proportion of these trainees were emotionally immature, low in ability, from poor and unhappy homes, and with tendencies to easy frustration and psychological unrest. Steps taken to cope with these problems are described, and suggestions are made for improving some of the factors involved in their adjustment to training. The authors conclude that recruitment of these younger age groups tends to flush out of the community a large proportion of youths who are having difficulties in adjustment, and that the psychologically sound care that should be available to trainees of all ages is even more urgently indicated the younger the age group involved.

*Putrid Empyema Without Foul Sputum.* H. NEUHOF AND D. STATS. *Surgery*, 18: 411, October, 1945.

The diagnosis of putrid empyema in the absence of foul sputum or other evidence of a pulmonary abscess is difficult. The lesion should be suspected and efforts at diagnosis persisted in when a given set of clinical manifestations are present. Prolonged delay in diagnosis may be fatal. The variable clinical manifestations are described. They consist primarily of outstanding and persistent chest pain, slight cough and expectoration, and an illness which is severe at least in the initial stage. Cough may be absent; the course may be chronic. The discovery of foul pus by aspiration of the pleura is the sole method of establishing the diagnosis. This disclosure will often be a surprise. Wide drainage of the main lesion and its ramifications will effect a cure unless the diagnosis has been delayed too long.

Although a pulmonary abscess is not demonstrable, we believe, for reasons which have been advanced, that a putrid pulmonary abscess is the precursor of "surprise" putrid empyema. Resumes are presented of 3 of the 15 cases on which the paper is based.

*Transverse Myelopathy Following Recovery from Pneumococcic Meningitis.* S. SIEGAL. J. A. M. A., 129: 547, October, 1945.

A woman aged 66 recovered from a fulminating type-six pneumococcus meningitis. Therapy consisted of penicillin both intrathecally and intramuscularly. Sulfadiazine was also given. Paraplegia, bladder paralysis and sensory loss below the 10th thoracic segment indicative of transverse myelopathy supervened several days after apparent recovery from the meningitis. There was no evidence of blockage of the subarachnoid space at any time. During a four month convalescent period there was little return of motor function. This serious and apparently permanent complication may be regarded as a natural although rare sequela of severe meningitis, only now recognized because of more effective methods of therapy in a disease formerly almost 100 per cent fatal. On the other hand it may have been due to too intensive and prolonged intraspinal treatment with penicillin. In view of the latter possibility, and particularly since recovery from pneumococcic meningitis has been reported with penicillin administered only by the intramuscular route, it would seem wise at present to limit intrathecal therapy to the first few days of the disease. Intraspinal dosage should be not more than 10,000 units per injection and emphasis should be placed upon high intramuscular dosage of penicillin.

*Hyperplasia of the Gums from Dilantin Sodium.* L. STERN. Alpha Omega Dental J., 39: 24, October, 1945.

The reaction of the gums to dilantin sodium is associated with hyperplasia of the gingivae. An analysis of changes in the gums of 68 patients treated at the Mount Sinai Hospital indicates that about half of the patients receiving the drug showed gingival alterations in response to dilantin. These changes were of several grades of severity, ranging from a granular, warty dotting of the gingivomucosal surface to a heavy overgrowth of the gingival margin with extension of soft tissue over the anatomical crowns of the teeth.

*Penicillin in the Treatment of Oral Lesions.* L. STERN. The Journal of the Second District Dental Society, 31: 3, October, 1945.

Penicillin topically applied was less effective in reducing postoperative pain, swelling, and other complications to the healing of oral wounds than sulfanilamide. However pain, lymphadenitis and fever associated with acute alveolar abscess resolved far more rapidly in a group of cases treated by intramuscular injection than similar cases treated with orally administered sulfathiazole or sulfadiazine. Acute submaxillary phlegmons were brought under early control with intramuscular injections of penicillin of 20,000 units q. 3 h, but incision for drainage was necessary. Penicillin therapy reduced the volume of pus discharging from fistulae in osteomyelitis of the mandible. When chemotherapy was discontinued, the volume of pus returned to its original profuseness. The usual clinical course of osteomyelitis was observed, with recovery delayed until all sequestra were exfoliated. Five of fourteen cases of fusospirochetal gingivitis responded favorably to penicillin.

*Some Aspects of Focal Infection.* L. STERN, JR. The Alpha Omega Dental Journal, 39: 20, October, 1945.

The problem of focal infection is presented from two aspects. The clinical problem, that which is concerned with the practical indications for the removal of suspected foci, especially teeth, must be solved by clinical experience with a great deal of conservatism. The theoretical aspect is discussed in more detail. Rosenow's early findings are by and large rejected, but recent evidence is then reviewed which possibly confirms the focal infection concept. The one bulk of evidence is empirical, dealing with bacteremias as produced by dental manipulations. The other bulk of evidence is derived from experimental

work by Schwartzman, Sanarelli, and others on local tissue reactivity. Finally, the experiments of Weisberger are presented, showing the artificial production of focal infection with *Streptococcus viridans* by means of immunologic phenomena similar to the Schwartzman reaction.

*The Procaine Esterase Test in Toxic Goiter and Carcinoma.* B. KISCH. *Exper. Med. & Surg.*, 3: 357, November, 1945.

77 patients from surgical clinics were investigated, concerning the procaine esterase index of their serum. The mean value of the PEI was 67, in 4 cases of non-toxic goiter it was 66, in 26 cases with clinical diagnosis of toxic goiter it was found to be 83.2 and in 6 cases of carcinoma of different organs it was found to be 41.7.

*Acute Diverticulitis of the Sigmoid in Pregnancy.* M. D. SCHNALL, L. E. PHANEUF, AND J. F. CONWAY. *Am. J. Obst. & Gynec.*, 50: 558, November, 1945.

A review of the literature for the past forty years does not reveal the description of a single case of acute diverticulitis occurring at the time of pregnancy and labor. It is possible that a number of such cases go undiagnosed and therefore the course of a patient with acute diverticulitis of the sigmoid with abscess formation and spontaneous resolution in pregnancy, labor, and in the puerperium is presented in some detail. The authors discuss the differential diagnosis of left lower quadrant pain in pregnancy, treatment of sigmoid diverticulitis, and the manner of obstetrical delivery in the presence of this disease.

*The Treatment of Early Syphilis with Penicillin.* W. LEIFER. *J. A. M. A.*, 129: 1247, December, 1945.

Each of 96 patients with early syphilis received sixty intramuscular injections of 20,000 units of penicillin in saline solution at three hour intervals, day and night, for seven and one-half days. A Herxheimer reaction occurred in 88 (91.6 per cent) of the patients, and also some minor cutaneous, gastrointestinal and febrile reactions: in no case was it necessary to suspend or interrupt treatment because of reactions. A relapse was observed in 8 (8.3 per cent) of the 96 patients, but 2 of these may have been reinfection. Relapse occurred in 1 (5.3 per cent) of 19 seronegative primary cases, in none of 34 seropositive primary cases and in 7 (16.3 per cent) of 43 secondary cases. Of 72 patients followed from twelve to twenty months, 70 were seronegative and I had a doubtful Kahn test of the blood at the last visit; the other patient relapsed in the thirteenth month, and he may have had a reinfection. The cerebrospinal fluid of 89 patients was reexamined six months or later following treatment; it was normal in 86, including 8 with abnormal pretreatment fluids: the 3 abnormal fluids were coincidental with a clinical or serologic relapse three to four months after treatment. Although the results of this study must be considered preliminary—and the optimum treatment schedule, particularly for secondary syphilis, is still to be worked out—the findings suggest that the eight day treatment of early syphilis with 1,200,000 units of penicillin does cure early syphilis.

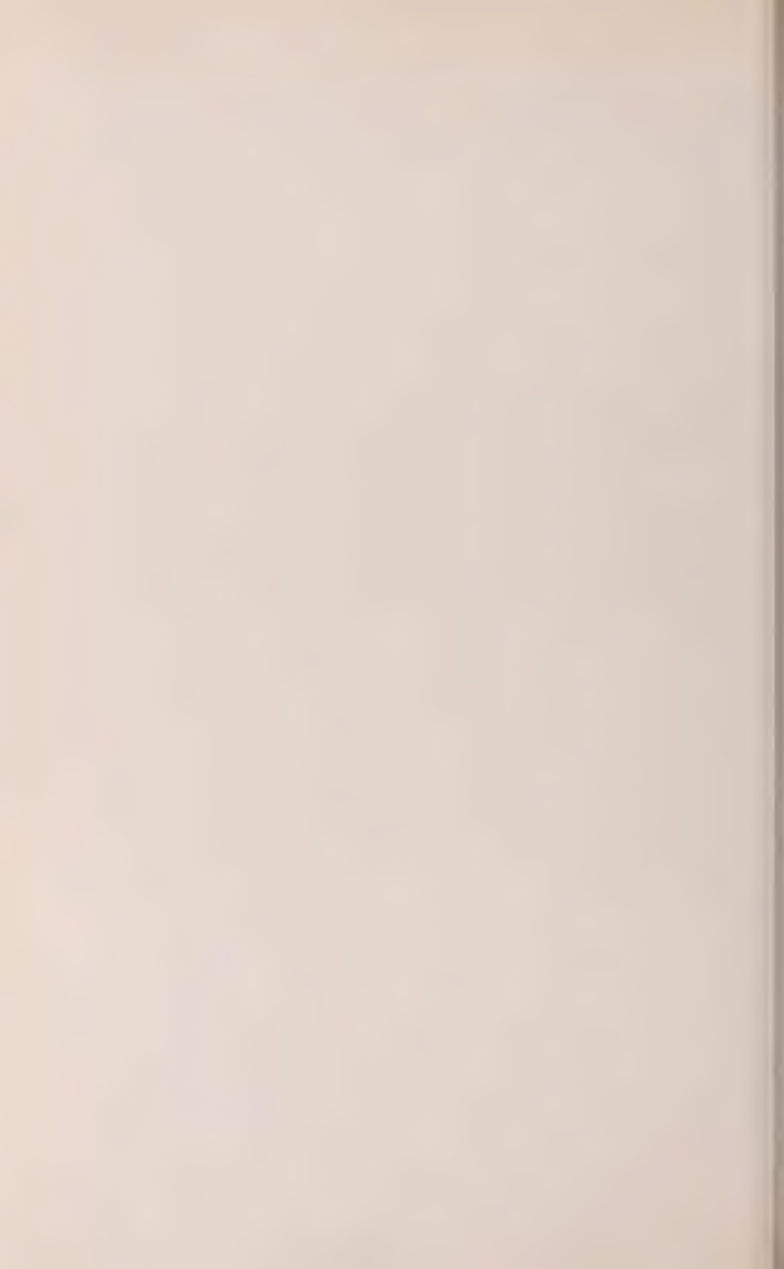
*Therapeutic Aspects of Uterotubal Insufflation in Sterility.* C. RUBIN. *Am. J. Obst. & Gynec.*, 59: 621, December, 1945.

In addition to its diagnostic value in sterility of tubal origin, uterotubal insufflation is also of therapeutic benefit. Its mode of action is, primarily, release of obstructed fallopian tubes by separating mucosal agglutinations, straightening tortuosities, dislodging mucus inspissations and separating adhesions. The therapeutic action of repeated insufflations in the presence of tubal obstruction is apparent when the initial pressure rise and the level at which pressure is maintained are lower than during the first insufflation. Improvement of the tubal status after repeated insufflation was obtained in 185 of 939 cases of tubal obstruction (19.79 per cent), in 238 of 917 cases of adherent and obstructed tubes (25.95 per cent) and in 15 of 134 cases of uterotubal patency and motility improved after two or three insufflations. Sixty-six (15.07 per cent) became pregnant. In order to determine the thera-

peutic effects of uterotubal insufflation, a statistical analysis was made of 590 cases of pregnancy occurring after insufflation in a series of 3,200 cases of sterility. The sources included 2,014 patients with primary sterility of which 358 (17.77 per cent) became gravid and 1,186 patients with secondary sterility of whom 232 (19.56 per cent) became gravid. Certain criteria were set up to eliminate chance and coincidence. A therapeutic result was deduced when the following conditions were met: 1. The age of the woman was 30 years or over. 2. The length of marriage was three years or longer. 3. No other therapeutic measure was employed. 4. The insufflation was done within the first two weeks of a last regular period. 5. No contraceptive precautions were taken for at least one year prior to the test. 6. Pregnancy followed within one month or at most two months after insufflation. 7. Pregnancy followed after repeated insufflation, a relatively lower pressure demonstrating improved patency during a second, third or fourth test. 8. Pregnancy followed the third month after one insufflation during which a high initial pressure was necessary and the tubes were found to be strictured or adherent.

Of the 590 women who became gravid, 146 were between 20 and 25 years old, 250 were between 25 and 30 years old and 184 (31.19 per cent) were 30 years of age or over. Length of marriage was from one to three years in 225 and longer than three years in 365 (61.86 per cent). Duration of sterility was from one to three years in 285, three to five years in 162 and longer than five years in 143. Contraception had been employed by 190 patients (32.2 per cent) at some time of their marital life; of these 39 had ceased contraceptive precautions for one year, 97 for two years and 54 from three to seven years before insufflation. The author noted that compared with the expected natural incidence of spontaneous conception after varying periods of sterility, the conception rate in his patients was increased threefold after three years of sterility, was greatly enhanced after seven years and proportionately improved after 10 years. In this series there were 316 patients with normally patent tubes (53.56 per cent), 135 with adherent tubes (22.88 per cent), 118 with strictured tubes (20.00 per cent) and 21 with spastic tubes (3.56 per cent). Initial pressure rise above 100 mm. Hg., evidence of impaired tubal patency, was noted in 247 patients (41.86 per cent). Repeated insufflations improved the tubal status in many of these cases before pregnancy occurred. Data regarding the time elapsing between insufflation and conception was noted in 573 cases. One hundred and fifty-eight patients became gravid within one month and 70 in from one to two months, making a total of 228 gravidities (38.64 per cent) within two months after insufflation.

In this series of 590 patients, there were 26 who fulfilled *all* the rigid criteria outlined above, i.e., they were over 30 years of age, were sterile for more than five years, took no contraceptive precautions for at least one year, resorted to no treatment other than insufflation and became pregnant within one month following this procedure. In addition, there were 66 in whom a therapeutic action of insufflation is suggested because pregnancy followed improved tubal status as a result of repeated insufflations. The author concludes that even though the element of chance may intrude to some degree, the evidence in this series indicates that, by relieving tubal obstruction, uterotubal insufflation exerts a therapeutic effect in female sterility.





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## THE TREATMENT OF EPILEPSY\*

H. HOUSTON MERRITT, M.D.

(New York, N. Y.)

*Historical review.* The modern approach to the treatment of epilepsy begins with the middle of the nineteenth century. While it is true that various drugs were used by the ancient and medieval physicians, the treatment methods of these times were mainly dietary restrictions, the invocation of supernatural powers and the administration of substances which had magical properties.

In his comprehensive monograph on the falling sickness, Temkin (1) gives the various forms of treatment of the disease from ancient times to the latter part of the nineteenth century. The list of remedies for seizures, which are noted in his monograph, includes preparations of gold and coral, oil of vitriol, mistletoe, valerian, oxide of zinc, silver nitrate, turpentine, indigo, belladonna, henbane, and inhalations of chloroform.

The drugs which were used in the latter part of the nineteenth century as listed by Spratling (2), included the bromides, which will be discussed more fully later, opium, codeine, borax (suggested by Gowers in 1879), chloral hydrate, amylene hydrate, nitroglycerin, chlorotone, zinc salts, urethane, solanum carolinense, simulo (made from a South American plant of the hyssop family), trional, iron, coal tar derivatives (phenacetin, antipyrin and acetanilid), and chloroform. The introduction of the bromides as a therapeutic agent in epilepsy resulted from an interesting observation of Locock. On the occasion of the presentation of a paper on the analysis of 52 cases of epilepsy by E. H. Sieveking (3) before the London Medico-Chirurgical Society on May 11, 1857, Dr. Charles Locock, (4) the presiding officer, remarked that since the seizures in epilepsy were often related to hysteria or the menses, he had been led to try bromide of potassium by an observation made by a German physician that it was capable of producing temporary impotence. He had 14 months previously prescribed bromides as a remedy in a case of epilepsy connected with sexual excitement and after all other medication had failed, the result had been an entire cessation of attacks. He had also tried the bromide of potassium in 14 or 15 similar cases, with failure in only one. Sieveking (5) states in his monograph on epilepsy, which was published in 1858, that he had tried bromide of potassium in epilepsy but that his experience with the drug did not allow him to draw any definite conclusions.

The next advance in the pharmacological treatment of epilepsy was the introduction of the use of luminal (phenobarbital) by Hauptmann (6), in 1912. This drug which had been introduced as a sedative and a hypnotic, was used by Hauptmann, an assistant in Hoche's Clinic in Freiburg, for these purposes in

\* Presented as part of a series of lectures entitled Recent Advances in Therapy, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on February 19, 1947.

From the Division of Neuropsychiatry, Montefiore Hospital and Department of Neurology, College of Physicians and Surgeons, Columbia University, New York.

epileptic patients and administered it in daily doses of 0.3 gram to patients with frequent and severe grand mal seizures. He reported favorable results in the cases, the number not stated, which he had treated for six months. There was a reduction in the frequency of the attacks and a decrease in the severity of the attacks that did occur. He noted no untoward side effects from the use of the luminal. In fact, there was general improvement in the health and nutrition of the patients who had suffered from over-dosage of bromides. He noted that sudden withdrawal of the drug would result in the precipitation of a number of seizures.

Between 1912 and 1937 researches in the therapy of epilepsy were directed toward the modification of the internal milieu by restriction of fluids and by dietary measures rather than by the administration of drugs. In 1921 Geyelin (7) demonstrated that fasting influenced the incidence of seizures in a certain number of the patients with epilepsy and suggested that the benefit was due to the acidosis induced by the fasting. This observation of Geyelin led to other methods of producing an acidosis. Wilder (8) at the Mayo Clinic demonstrated that a diet high in fat and extremely low in carbohydrate was as effective in producing acidosis as fasting. Wilder proposed the diet on the theory that acetoacetic acid should behave pharmacologically as an anesthetic. Other observers believed that a high fat diet owed its therapeutic value to its action on the acid-base equilibrium by correcting an abnormal tendency toward the spontaneous development of alkalosis.

Data which showed disturbance in the water-balance in patients with epilepsy were presented by Gamble (9) in 1923. McQuarrie (10) in 1929 demonstrated that a negative fluid balance tended to reduce the frequency of seizures. The greatest advocate of the dehydration therapy, however, was Temple Fay (11) of Philadelphia. The excessive restriction of fluid intake necessary to maintain a negative fluid balance negated any wide acceptance of this form of treatment.

In 1937 a new method of testing the anticonvulsive activity of drugs in animals was devised by Putnam and Merritt (12). By this method, Merritt, Putnam and Schwab (13) tested a large number of compounds and found a number of them to have an anticonvulsant activity greater than those already in common use. One of these compounds, sodium diphenyl hydantoinate (phenytoin sodium, dilantin sodium, epanutin) (14) was introduced into the treatment of epilepsy. The results obtained with sodium diphenyl hydantoinate have led to the successful trial of other hydantoin derivatives (15) and to the synthesis of another compound known as 5,5,5-trimethyloxazolidine-2,4-dione (tridione).

*Types of seizures.* Epilepsy is commonly divided into two groups, symptomatic and idiopathic. This division is of limited value since it implies that we understand the mechanism of the seizures in patients with known lesions in the brain. On the other hand, the concept that organic lesions play a role in the causation of seizures, is of value in that it emphasizes the need of a thorough medical study of the patient. Needless to say, this medical study of the patient should be supplemented by an investigation of the personality of the patient.

A division of the phenomena which occur during epileptic seizures is of value in directing the therapy. On basis of these phenomena the seizures may be divided into three groups: petit mal, grand mal (including Jacksonian seizures), and psychic equivalent or psychomotor attacks.

Petit mal attacks, which are characteristically a disease of childhood, are accompanied by transient clouding of consciousness lasting for only a few seconds, with or without minor movements of the head, eyes and extremities, and loss of muscular tone.

The phenomena which occurs in a grand mal attack may be quite varied. Characteristically these attacks are ushered in by a warning (aura) and are followed by a sudden loss of consciousness with tonic-clonic spasms of the musculature, with or without urinary and fecal incontinence.

Psychic equivalent, or psychomotor attacks, are terms used to describe a heterogenous group of epileptiform disturbances which do not conform to the classical grand mal or petit mal types of seizure. The milder psychomotor attacks are often confused with petit mal attacks but they differ from the latter in that the duration of the period of mental cloudiness is greater and the range of muscular movements is much more wide spread. They differ from the grand mal attacks in that the patient does not fall to the ground in a tonic-clonic seizure with complete loss of consciousness. In the severer form of psychic equivalents, the patient may be in a clouded state for many hours and perform acts of which he is entirely unaware.

It has been shown that with a seizure there are disturbances in the electrical activity of the cortex which is characteristic for each of the three forms of convulsive seizures described above. The electroencephalogram is not only of value in recording the changes that occur coincident with attacks, but also in registering abnormal activity in the interval between attacks. The finding of an entirely normal electroencephalogram does not, however, exclude the diagnosis of epilepsy. Approximately 15 per cent of patients with epilepsy, will have a normal record if only one tracing is taken in the seizure-free interval. On the other hand, the presence of abnormalities in the electroencephalogram is not in itself diagnostic of epilepsy since such changes are found in 10 per cent of the normal population.

*Treatment.* Success in the treatment of patients with epilepsy depends to a great extent on the control of the seizures. The economic, social and psychological rehabilitation of the patient can only be attained when the seizures have been eliminated or reduced to a minimum. The discussion in this presentation is, therefore, limited to the consideration of the methods which are of value in the control of seizures. At the present time, the chief means of controlling seizures is the administration of anticonvulsant drugs. The administration of anticonvulsant therapy must be preceded by a thorough medical and psychological study of the patient. Any factors of importance in the causation or precipitation of the seizures should be treated.

Whenever convulsive seizures are associated with a surgically removable lesion of the brain, such as tumor or abscess, removal of such a lesion is indicated. It must be remembered, however, that the relief of convulsive seizures will result

in only about fifty per cent of cases of meningioma of the brain and in a much smaller percentage of cases of glioma or abscess of the brain. In such cases, further treatment with drugs is necessary.

In addition to the removal of expanding lesions, surgery has been advocated for the removal of cortical scars secondary to cerebral trauma, vascular lesions and birth injuries on the assumption that such scars produce irritation of the neighboring cortex and act as a trigger mechanism for the seizures. Good results of such excisions have been obtained by a number of neurosurgeons. This treatment should be limited to the group of patients with focal attacks which do not respond to medical therapy. In addition, the excision of such lesions should be performed only by neurosurgeons who have the facilities for adequate localization of the lesion. Medical treatment must also be used in these patients after operation. It is difficult to evaluate the results that have been obtained by surgery in these cases because of the fact that these patients are treated with anticonvulsants after the operation.

The excision of isolated foci of abnormal electrical activity as shown by the electroencephalogram is still in the experimental stage and is not to be advised as yet, since it is possible that the excision of such abnormal foci will only result in the shifting of the abnormality to another region of the cortex.

Operations other than on the central nervous system are not advisable unless indicated for reasons apart from the occurrence of convulsive seizures. Removal of the cervical sympathetics or portions of the large intestine, operation on the sinuses, etc. have no effect on the ultimate course of the seizures. Removal of tumors of the pancreas is, of course, necessary when attacks are definitely proved to be related to hyperinsulinism. Removal of the carotid sinus may be of benefit in patients with carotid sinus syncope.

It is only rarely that the elimination of causative factors will result in the complete disappearance of attacks; in the vast majority of patients, control of the attacks require in addition, regulation of the physical and mental hygiene and the administration of anticonvulsive remedies. The decision regarding which drugs should be used in a given case depends on the type and frequency of the attacks. It is important to remember that, if satisfactory results are not obtained with one form of medication, a change should be made to another drug or two or more drugs used together.

Phenobarbital can be tried first in the treatment of patients with infrequent grand mal seizures because of the high therapeutic index and the relatively low toxicity of this drug. If satisfactory results are not obtained, phenytoin sodium should be tried. A combination of phenobarbital and phenytoin sodium is often more effective than either one of the drugs when used alone. It must be remembered that in using these drugs in combination, a full therapeutic dose of each drug must be used. In patients with frequent grand mal seizures or attacks of the psychic equivalent or psychomotor type, phenytoin sodium is the drug of choice. The treatment of petit mal attacks in children has not been standardized as yet. Glutamic acid has been reported to be of value in the treatment of petit mal attacks. We have not been impressed with the results



obtained with this form of therapy. Preliminary experiments with tridione (an oxazolinedione derivative) have given encouraging results.

For the average adult the initial dose of phenobarbital should be  $1\frac{1}{2}$  grains daily. This can be given at bed time. If after a trial period of two weeks or as long as is necessary to determine whether this dose is effective, further increases can be made in the dosage until the patient is taking as much as  $4\frac{1}{2}$  to 6 grains per day. If this amount of the drug is not sufficient to control the seizures it is probable that a further increase will not be of value. In children, the dose of phenobarbital should be in proportion to weight but it has been found that children are able to tolerate and require almost as large a dose as adults. It is therefore advisable to give children, over six or seven years of age, the minimum dose of  $1\frac{1}{2}$  grains per day.

Phenytoin sodium (dilantin sodium, 5,5-diphenylglycolyl urea), has the advantage over phenobarbital and the bromides in that it has very little or no hypnotic activity. The regulation of the dosage is more difficult, however, and minor toxic symptoms are more frequent (16). The toxic symptoms are not serious and it is almost impossible for a patient to take a fatal dose of the medicine.

In the average adult, the initial dose should be  $1\frac{1}{2}$  grains (0.1 gram) of phenytoin sodium three times daily. If any seizures occur after two weeks of this dosage it should be increased to 6 grains (0.4 grams) daily. Further increases in the dosage should be by increments of  $1\frac{1}{2}$  (0.1 gram) until the maximum dose of 9 grains (0.6 grams) daily, is reached. In the majority of adults 6 grains (0.4 grams) is the optimum dose. In children over 12 or 14 years, the average dose is  $4\frac{1}{2}$  to 6 grains (0.3 to 0.4 grams) and in younger children 3 to  $4\frac{1}{2}$  (0.2 to 0.3 grams). The medicine can be given in divided doses spread out through the day or it can be given all in one dose at bed time. The drug is quite alkaline and it may cause gastric upsets. This can be prevented by giving the drug along with the meal or with some food.

Various derivatives of the hydantoins have anticonvulsant properties (15). In some patients one of these hydantoin derivatives may be more effective in controlling grand mal or psychomotor seizures than either phenobarbital or phenytoin sodium. The author has reported the results with the use of several of these hydantoin compounds (15).

Kozol (15) reported on the use of 3-methyl-5,5-phenylethylhydantoin (phenantoin, mesantoin) in the control of convulsive seizures. Of 104 patients who were treated for an average of ten months, 19 per cent were seizure free (3-22 months) and 41 per cent were greatly or moderately improved. The average dose for children was 0.4 gm. daily, and for adults 0.6 gm. The maximum daily dose was 1.0 gm. The drug was often used in combination with phenytoin sodium. The most common symptoms of overdose was drowsiness. Toxic rash also developed in some patients. A number of cases were cited in which good results were obtained in patients previously uncontrolled with phenytoin sodium (alone or with phenobarbital), but no precise comparison of the efficacy of phenytoin sodium and mesantoin was attempted. The use of these various hydantoin derivatives

is still in the experimental stage and none are available on the open market as yet.

Bromides are rarely used in the treatment of epilepsy at the present time. They are, however, occasionally effective when other forms of therapy fail. The average dose for an adult is 15 grains (1 gram) of the sodium or potassium salt, three times daily with proportionate doses to children according to size. In the absence of toxic symptoms this dose can be increased to a maximum of 30 grains (2 grams) three times daily. The chloride intake must be kept at an adequate level to prevent undue replacement of chloride ion in the body fluid by the bromide. Facilities for the determination of the bromide content of the serum should be available. The effective level may be as low as 100 mg. 100 cc. in some patients, whereas 300 mg. 100 cc. may not be effective in others. Toxic symptoms usually develop with a concentration of 150 mg. or greater. The chief objections to the use of bromides lie in the frequency of the development of skin rash and their reputed tendency to produce mental dullness.

Since phenytoin sodium and the other hydantoin derivatives have very little sedative effect, it is possible to use one of them in combination with phenobarbital or bromides. These combinations (16) are of value when the administration of one of the drugs is not effective or when the effective dose of phenytoin sodium alone produces toxic symptoms. The doses of the combination must be worked out according to the tolerance of each patient. Three to 5 doses a day of a combination of  $1\frac{1}{2}$  grains (0.1 gram) phenytoin sodium with  $\frac{1}{2}$  grain (0.06 gram) of phenobarbital, of 15 grains (1 gram) sodium bromide, are usually required in the more resistant cases.

Preliminary experiments with tridione (3,5,5-trimethylxazolidine-2,4-dione) (17) have given encouraging results in the treatment of petit mal attacks. The use of this drug is accompanied by a cessation or reduction in frequency of petit mal attacks in approximately 50 per cent of the cases. In a few patients the cessation of attacks is accompanied by a decrease in the abnormalities in the electroencephalogram. In such patients it is sometimes possible to discontinue the use of the drug without recurrence of the petit mal seizures. The drug is of no value in the control of grand mal or psychomotor seizures. If patients are subject to one of the latter types of seizures, as well as petit mal, phenytoin sodium or phenobarbital should be given along with the tridione.

The dosage of tridione for the treatment of petit mal varies from 0.3 to 2.0 grams daily, starting with 0.3 gram and gradually increasing the dose until the seizures are controlled or toxic symptoms appear. Among the toxic symptoms are skin rashes, which require a cessation of the treatment, and visual symptoms—an unusual sensitivity to light. This latter symptom is apt to develop in adolescent or adult patients and is uncommon in young children. The photophobia is not accompanied by any change in visual acuity and disappears when the medicine is discontinued.

Two cases of fatal aplastic anemia following the exhibition of tridione for periods of six and ten months have been reported (18). Prolonged use of the drug may also be accompanied by a decrease in the percentage of polymorphonuclear leucocytes in the blood without an absolute decrease in the total number

of leucocytes. Although it is not known whether the observation of any precautions will make it possible to prevent serious or fatal changes in the blood, it is recommended that routine blood count be made monthly in patients using tridione. The drug should be discontinued if any significant changes are found.

*Treatment of status epilepticus.* Patients who are subject to seizures may have attacks so frequently that they do not recover from the coma produced by one attack before the next attack supervenes. The patient remains in coma for 12 to 24 hours during which time there may be many convulsive seizures. The attacks may cease spontaneously and the patient recover consciousness after a period of 24 to 48 hours, or death may occur as the result of the repeated attacks. The likelihood of the latter eventuality is so great that vigorous therapeutic methods aimed at terminating the seizures are justified. Good results in regard to termination of the attacks can sometimes be obtained by anesthetizing the patient with one of the volatile anesthetics such as chloroform or ether. Termination of the seizures is more certain with the injection of sodium phenobarbital or paraldehyde intravenously with less risk of pulmonary complications. It is important that a large dose be given at the first injection because best results are obtained when the full amount is given in one, rather than in divided doses. For status epilepticus in adults 0.4 to 0.8 gram (6 to 12 grains) of sodium phenobarbital dissolved in distilled water should be injected intravenously or 3 to 6 cc. of paraldehyde injected intravenously. The dosage for children should be from 0.2 to 0.4 gram (3 to 6 grains) of sodium phenobarbital or 2 to 4 cc. of paraldehyde according to the size of the child.

#### SUMMARY

Since we do not know the nature of the basic organic or physiologic disturbance which is responsible for the occurrence of convulsive seizures, our treatment of epilepsy at the present is empirical and is directed mainly toward prevention of the seizures. This empirical treatment includes elimination of any organic lesions in the central nervous system or elsewhere in the body, regulation of the physical and mental hygiene, and the administration of anticonvulsant drugs. The success of the treatment is dependent to a great extent on the skill with which anticonvulsant drugs are administered. The dosage of the various drugs must be regulated according to the needs and tolerance of each individual patient. Failure to obtain good results is often due to inadequate dosage.

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## PHYSIOLOGIC THERAPY IN DISEASES OF THE RESPIRATORY SYSTEM\*

ALVAN L. BARACH, M.D.

(New York, N. Y.)

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York City*

In selecting the term "physiologic therapy" I had the aim of emphasizing forms of treatment that were largely outgrowths of studies on the pathologic physiology of respiratory illness. Its basic purpose may be defined as the attempt to correct deviations from the normal functioning of the lungs and bronchi and to eliminate, whenever possible, reversible pathology in these organs.

Inhalation of oxygen is an early example of physiologic therapy since it has long been recognized as a specific remedy for impaired lung function. When administered to normal subjects at moderately high altitude, the breakdown in the respiratory, circulatory and central nervous systems as the result of progressive anoxia is prevented. Clinical disorders of breathing have especially lent themselves to measures of this kind that improve physiologic behavior of the lungs and bronchi. Anoxic dyspnea in clinical disease has often been successfully combatted by inhalation of oxygen enriched atmospheres, manifested by decrease in pulmonary ventilation, fall in pulse rate, and disappearance of cyanosis.

The therapeutic use of gases includes carbon dioxide, which has the physiologic objective of stimulating breathing, especially in the respiratory depression of carbon monoxide poisoning and in the preventive or actual treatment of post-operative pulmonary atelectasis. Besides its employment for the treatment of hiccough, this gas is now rarely employed as an aid in the management of clinical dyspnea.

Administration of helium mixed with oxygen, in a proportion of 75-80 per cent helium with 25-20 per cent oxygen, was advocated to decrease the physical effort of breathing in obstructive dyspnea, such as occurs in asthma and constrictive lesions of the larynx, trachea and bronchi. In addition, this lighter than air mixture, as a consequence of its higher diffusion capacity, has been shown to penetrate alveoli that may be relatively impermeable to air or oxygen. Inhalational therapy also includes introduction into the lungs and bronchi of bronchodilator, broncho-vasoconstrictor and antibiotic aerosols. Nebulized epinephrine and neosynephrine have been employed to increase the diameter of the respiratory passageway by the production of local broncho-dilatation and broncho-vasoconstriction. The sulfonamides, penicillin and streptomycin are currently used as therapeutic aerosols in the treatment of broncho-pulmonary and sinus infections.

I propose this evening to illustrate the value of another form of physiologic therapy of respiratory disease that involves the use of various types of pressure.

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Alternating pressure has long been employed for resuscitation. In more recent years positive pressure has been shown to have significant physiological advantages in the treatment of obstructive dyspnea and pulmonary edema and more recently in the anoxia of very high altitude. Equalizing the pressure on both sides of the chest wall, in combination with alternating pressure, will be especially dealt with as a method which immobilizes the lungs of the living subject, providing a hitherto unachieved form of lung rest that has now been shown to be of significant value in the treatment of pulmonary tuberculosis. Finally, an instance of the use of negative pressure in the nasal accessory sinuses will be illustrated as a method of local introduction of penicillin and other therapeutic aerosols.

It will be seen that a variety of physiologically directed procedures have developed from the study of the mechanics as well as the chemistry of breathing in respiratory illness, sufficient, it would seem, to justify the title of this presentation, *Physiologic Therapy in Diseases of the Respiratory System*.

In 1878 Oertel employed 20 to 100 inspirations of air compressed to  $\frac{1}{80}$  to  $\frac{1}{50}$  of an atmosphere excess pressure in the treatment of severe asthma. He reported that dyspnea was relieved, inflation of the air cells checked, and the secretion of sero-mucous fluid into the finer bronchi was diminished. He believed that this was due to decrease in the inspiratory dilatation of the thorax during partial occlusion of the bronchioles, a concept which our studies on pressure breathing in obstructive dyspnea, carried out many years later, appeared to confirm. Although Haven Emerson had demonstrated in 1909 that pulmonary edema in rabbits, produced by intravenous injection of adrenalin, was abolished by artificial respiration, the clinical use of this procedure did not take place until Poulton in England, and my colleagues and I began to study positive pressure respiration in 1935. The inhalation of oxygen (or air) under a positive pressure of 3 to 13 cm.  $H_2O$  was found to have a decidedly favorable effect in conditions of obstructive respiration and pulmonary edema. The studies which support this contention will be reviewed.

When experimental animals inspire through a constricted orifice the negative pressure within the lungs becomes progressively elevated and is itself the precise cause of the subsequent development of pathological changes in the lungs and bronchi, such as congestion and edema, emphysema and, finally, impairment of the circulation. If air is then breathed under a pressure of 6 cm. of water, the pathologically elevated negative pressure within the lungs is decreased as the atmosphere is gently forced past the point of constriction. During expiration the presence of increased positive pressure increases the diameter of the bronchi, diminishing bronchial constriction.

Although more marked relief of obstructive dyspnea takes place with an atmosphere of 80 per cent helium and 20 per cent oxygen during pressure breathing, a considerable degree of relief, between 50 and 60 per cent of that obtained with the helium-oxygen mixture, is provided by breathing oxygen under continuous positive pressure. When pure oxygen is employed clinically, for the treatment of bronchial asthma, pulmonary edema, or obstructive lesions in the tracheo-bron-

chial tree, one hour periods of inhalation of air, 50 per cent oxygen or 80 per cent helium-20 per cent oxygen mixtures should be provided at intervals of 6 to 8 hours in order to avoid the hazard of irritation to the lungs. The treatment of obstructive dyspnea is especially aided by positive pressure during *inspiration* since the significant pathological event is the inspiratory elevated negative intrapulmonary pressure; this is not relieved when pressure is applied in expiration only.

In the treatment of acute pulmonary edema etiological factors determine the selection of therapeutic measures appropriate in the individual case. When it takes place as a result of alteration in the permeability of the pulmonary capillaries, as occurs in patients with lobar and bronchopneumonia, the inhalation of oxygen under a positive pressure of 3 to 6 cm.  $H_2O$  has now been proven to be a decisive and specific technique for the clearing of moisture in the lungs. Although a continuous pressure, such as is provided by the pressure hood, or by a demand mask apparatus, is more effective and comfortable, the inhalation of oxygen with a mask that provides positive pressure on expiration only is also generally capable of terminating the condition. When expiration is conducted against a pressure of 3 to 4 cm.  $H_2O$ , while inspiration is at atmospheric pressure, the subjective effort of breathing against pressure is experienced by the patient as effortful. However, an even higher pressure, such as 5 or 6 cm.  $H_2O$  continuously provided in inspiration and expiration, is not found to be uncomfortable since the proprioceptive reflexes from the lungs are not so stimulated by a continuity of heightened pressure.

Approximately one-half the applied mean pressure is taken up by the elasticity of the bronchi and the lungs, and one-half is applied directly to the outer walls of the pulmonary capillaries, thus exerting a direct opposing physical force that tends to counteract the hydrostatic pressure within them and, therefore, the tendency to transmit serum into the alveoli. The venous pressure is correspondingly elevated, in some instances there is a decrease in the amount of blood entering the right heart, in that way diminishing pulmonary congestion and permitting the heart to work on a smaller volume of blood.

During the war much higher pressures, in the order of 20 cm.  $H_2O$ , were used with a demand mask apparatus in order to increase the partial pressure of pure oxygen at high altitudes. In this way a gain of approximately 2500 feet in ceiling was secured, for example from 42,500 feet to 45,000 feet.

Anoxia is itself a contributing cause to pulmonary edema in many clinical entities in which it occurs, and the inhalation of oxygen is thus an indicated measure. However, application of positive pressure has been demonstrated to be a specific remedy in terminating the condition when oxygen itself has been useful simply in relieving anoxia and maintaining a more nearly normal arterial oxygen saturation. The reason for this may be found in the reaction of patients who develop sero-mucous exudation in the bronchi following tracheotomy for laryngeal obstruction. The sudden absence of the back pressure to which the pulmonary capillaries and bronchial mucous glands were accustomed as the patient exhaled against a positive pressure (caused by constriction in the airway) results in persistent exudation of serum and mucus that requires ordinarily inter-

mittent suction. When patients with this condition are treated by breathing air against a positive pressure of 4 to 6 cm. of water, inspiration being free, the continued formation of serum and mucus is stopped. Gradual decrease in the pressure accustoms the pulmonary capillaries and the mucus glands in the bronchi to atmospheric pressure. Similarly, when pulmonary edema has once begun in a patient with pneumonia, the chemical state of the gaseous equilibrium in the blood is favorably influenced by inhalation of oxygen, but the exudation of serum may not cease until positive pressure is applied.

Turning from the application of pressure for the treatment of obstructive dyspnea and pulmonary edema, I wish to describe a use of pressure in which all voluntary breathing is dispensed, in which no movement of the lung takes place despite the maintenance of a normal pulmonary ventilation. The first example of artificial respiration by mechanical means was that of Thunberg in 1927 who placed patients with respiratory paralysis in a chamber in which an alternating pressure of  $\frac{1}{6}$ th of an atmosphere was produced. This resulted in an increase and decrease of the density of the atmosphere within the chamber equivalent to an inflow and outflow of 500 cc. of air a minute in and out of the lungs. In our investigation of this method in experimental respiratory paralysis in animals induced by nembutal, the arterial oxygen saturation gradually fell, because of an inadequate exchange of air within and without the lungs. It appeared from these observations and from subsequent experience with patients exposed to such a chamber that the positive pressure wave compressed the chest to an extent slightly greater than the subsequent expansion due to negative pressure. After a period of residence in alternating pressure alone, the patient felt compelled to take an inspiration, as if the chest had been slightly, but progressively compressed. Furthermore, the resistance of the tracheobronchial tree was a variable factor that decreased to a slight extent the initial pressure within the lungs as compared to that applied to the outer chest wall. Finally, there was a momentary delay in the arrival of pressure within the lung as compared to that which was immediately exerted on the outer thorax. This inequality between the initial positive and negative pressure inside and outside the lungs was then compensated for in patients who had pulmonary tuberculosis. However, in patients with asthma and pulmonary emphysema, in whom the chest is alternately compressed and expanded and because of the increased bronchial resistance, maintenance of equalizing pressure was impossible.

In a specially constructed apparatus an opportunity was afforded to equalize the pressure within and without the chest, as well as on the upper and lower surfaces of the diaphragm. When air was admitted first into the head end of a chamber, and then entered the body compartment through a constriction about the neck, a delay in the arrival of pressure to the outer chest wall was obtained similar to the delay which took place in the arrival of the air wave within the lungs; at the same time a decrease in pressure was obtained by the air wave passing through the constricted orifice at the neck which was comparable to the initial decrease in the pressure produced by the tracheobronchial passageway itself. In this way, similar pressures were applied at the same time to the inside and outside of the chest wall.

Air enters and leaves the lungs through a variation in its density. During the negative phase expansion of air within the lungs results in elimination of carbon dioxide and during the positive phase compression of air within the chamber and within the lungs produces the equivalent of an inlet of 500 cc. of air containing 21 per cent oxygen. The resistance of the tracheobronchial tree is effective at the very start of the positive and negative phases. By observation on animals in which needles were placed within the intrapleural space and on the chest wall, the lag in the arrival of the pressure wave was determined and its amount calculated to be between 4 and 5 cm. of water. Equalizing pressure, therefore, refers to the

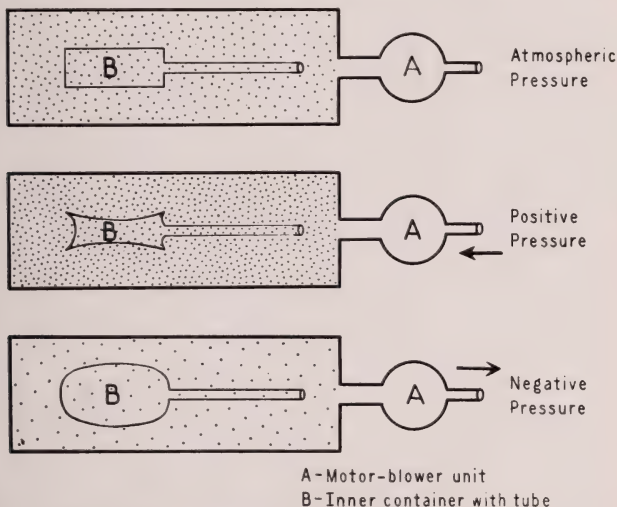


FIG. 1. Effects of alternating positive and negative pressure on a container with flexible walls and a tube connection. Concentration of gas molecules is increased and decreased as air enters and leaves the outer chamber. Walls of container are initially compressed and expanded due to delay and diminution of pressure passing through the constricting tube connection.

mechanics of decreasing and delaying the initial pressure arriving at the outside of the chest wall during the positive phase until a similar pressure can be built up within the lung and a reversal of this procedure during the negative phase. The accompanying diagrams (figs. 1 and 2) illustrate the mechanics of equalizing pressure as compared to alternating pressure.

The significance of this employment of pressure is that a patient with pulmonary tuberculosis may be treated for periods of 10 hours a day with actual lung rest, a pulmonary immobility not provided by rest in bed or by pneumothorax, in both of which movements of the lung take place. It is not our purpose in this

presentation to elaborate on the clinical response of the procedure, but it may be mentioned that therapeutic results of a specific character have taken place in patients with advanced bilateral tuberculosis and moderately advanced tuberculosis, including the closure of cavity and the clearing of infiltration in cases that were unresponsive to previous methods of treatment.

Finally, I wish to refer to the use of an alternate negative and relatively positive pressure that has been applied to the nasal accessory cavities with purpose of introducing nebulized drugs. The aim of aerosol therapy in diseases of the respiratory tract is to develop a high local concentration of the drug in the area

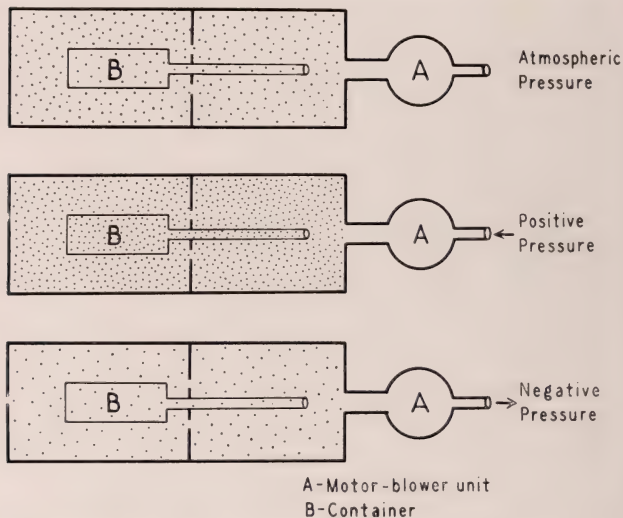


FIG. 2. Immobilization of walls of container produced by partition at entrance of chamber. Partition retards pressure until air has passed through tubal connection so that equal pressures are simultaneously exerted on the walls of the container in positive and negative cycles.

of the disease process. I cannot here refer to the extensive studies of Segal, Olsen and others, but I may point out that intramuscular injection of penicillin is at times not effective in overcoming bacterial infection of the lungs and bronchi. In illnesses such as empyema, and also in purulent infections within the sinuses, penetration of the antibiotic to the area where bacteria growth is taking place is especially limited and inadequate. When penicillin is inhaled through the nose by tight fitting glass nosepieces, a small amount of the aerosol enters the antra, in part through deposition on the orifices and in part through the negative pressure developed by inhaling an atmosphere past the orifice. A venturi-like action



presumably takes place which is the occasion for ventilation of the nasal accessory cavities. However, the degree of penetration of penicillin aerosol and the degree of ventilation of the sinuses in ordinary nasal respiration is generally insufficient to accomplish a curative result in purulent sinusitis.

An apparatus was, therefore, developed which produced intermittent negative pressure in the nose by the passage of oxygen through a venturi. The distal end of the venturi tube was connected with a nebulizer that produced a fine mist of penicillin as oxygen flowed through it. The side-arm developed a negative pressure which was varied from 50 to 80 or more mm. Hg, depending on the flow of oxygen. When the nasal passages were connected with the side-arm of the venturi a negative pressure of approximately 60 mm. Hg was produced in the antra as measured by a manometric reading from a dental fistula. As a result of inhalation of 50,000 units of penicillin aerosol with intermittent negative pressure applied to the nasal passages, and to the antra and other sinus cavities, a repeated replacement of air within the sinuses with a penicillin mist was produced. Substantially larger amounts of penicillin were found within the antra than took place during nasal respiration of penicillin aerosol without negative pressure. These observations, made by Talbot, Garthwaite, Rule and myself, in a study of deposition of penicillin within the sinus cavities, were confirmed by clinical evidence of recovery from both acute and chronic sinusitis. Although somewhat complicated valves were initially devised for the production of negative pressure, it has been recently found that no sinus valve is necessary; the venturi may be directly connected to the glass trap and nosepiece outfit. When the venturi is closed by the thumb, oxygen goes through the nebulizer, creating a dense mist of penicillin in the nasal passages. When the thumb is removed from the vertical end of the venturi, suction is produced, thus achieving intermittent deposition of penicillin in, and ventilation of, the various accessory sinuses.

#### SUMMARY

Physiologic therapy of respiratory illness at first utilized inhalation of oxygen to combat the functional pathology produced by anoxia. Subsequently, other therapeutic gases were employed, such as carbon dioxide, for the respiratory depression produced by carbon monoxide poisoning, helium in the treatment of obstructive dyspnea, and the therapeutic aerosols for local bronchodilator and antibiotic treatment. The significance of pressure applied to organs of breathing has been recently investigated by studies of the mechanics of breathing and patho-physiological conditions arising during the course of respiratory disease.

The following uses of various types of pressure have been described to illustrate the widening horizon of physiologic therapy of diseases of respiration:

1. Continuous positive pressure in the treatment of obstructive dyspnea and pulmonary edema;
2. equalizing the pressure on the inner and outer surface of the chest wall to produce arrest of lung movement, providing a new type of local lung rest for the treatment of pulmonary tuberculosis;
3. intermittent negative pressure applied to the accessory nasal cavities by which air within the sinuses is replaced with a penicillin mist for the treatment of acute and chronic purulent sinusitis.

# TUMORS OF THE TWELFTH NERVE

## REPORT OF TWO CASES<sup>1</sup>

BENEDICT J. BERNSTEIN, M.D.

AND

ALVIN I. GOLDFARB, M.D.

[New York, N. Y.]

Tumors arising in the hypoglossal nerve are rare. Haase (1), reviewing the literature for such tumors, found as recently as 1945 only four recorded instances, and only two of these were within the cranium. He added two new cases of intracranial neurinoma of the hypoglossal nerve, which were verified at autopsy.

This report is concerned mainly with hypoglossal nerve tumors of intracranial origin, and brief reference will be made to those extracranial in location. Neither of the two reported extracranial tumors, for obvious reasons, displayed any neurological signs and even the tongue was not affected prior to surgical intervention. However, it is known that the twelfth nerve is occasionally implicated together with other cranial nerves by extracranial tumors occurring in their extracranial course as in the syndromes of Vernet (2) and Villaret-Collet (3). (The latter is known also as the syndrome of the condyloid-lacerum posterius foramina.) In these syndromes individual nerves or combinations of the ninth, tenth, eleventh and twelfth cranial nerves and the postganglionic fibers of the cervical sympathetic may be affected. In these clinical constellations, however, there are usually no signs or symptoms of increased intracranial pressure or brain stem involvement although tumors in the jugular foramen may develop intracranially and provoke such symptoms (4).

In contradistinction to the foregoing syndromes the four cases of tumors affecting the intracranial part of the hypoglossal nerve displayed such symptoms and signs, i. e. headache, papilledema, nystagmus, and sensory or motor disturbances.

### CASE REPORTS

*Case 1. History.* (Adm. #524540, P.M. #12905) A woman, aged 38 years, began early in 1941 to be troubled by cough, headache and nausea. The headache was usually brought on when she looked upward, and when she sneezed or coughed. In October of 1942 she became subject to frequent attacks of dizziness, and she often complained of a tingling sensation in her fingers. In August 1942 atrophy and fibrillations on the right side of her tongue were noted. Eight months later (February 1943) she began to be troubled by hiccup. At the same time she began to have attacks of dizziness whenever she bent over or looked upward. In May 1944, about three years after the onset of the first symptoms, it was noted that she held her neck and head stiffly and was unsteady in her gait. Three months later her headaches began suddenly to be very severe and were accompanied by nausea. In view of this development a previous diagnosis of amyotrophic lateral sclerosis was abandoned and brain tumor affecting the medulla oblongata was now seriously considered. She entered the hospital on August 28, 1944, three and a half years after the onset of her first symptoms.

<sup>1</sup> From the Neuropathological Laboratory and Neurological Service, Mount Sinai Hospital, New York. Presented at the Neurological Conference, March 11, 1946.

*Examination.* The patient held her head and neck rigidly and resisted passive movements of the head in all directions. There was a fine nystagmus on left lateral gaze. The disc margins were somewhat blurred; the retinal veins were full; the arteries were constricted. There was bilateral corneal hypesthesia. The tongue deviated to the right, and its right half was atrophied. Change of position of the head caused marked flushing of the right side of the face. The patient walked guardedly for fear that unrestricted motion or change of position of the head might precipitate vertigo.

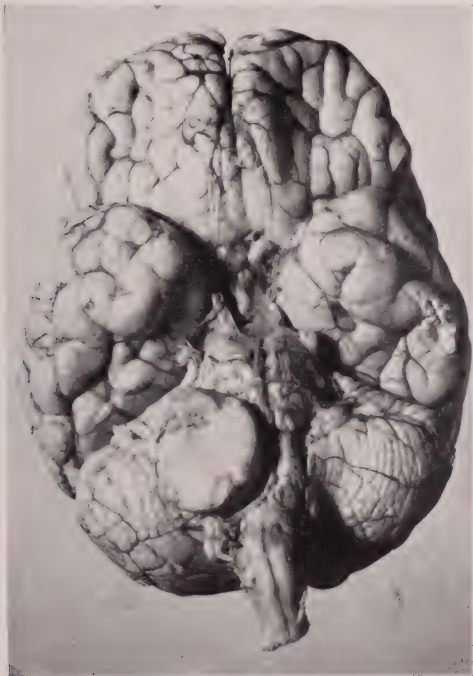


FIG. 1. Case 1, gross appearance of the base of the brain

*Laboratory data.* Lumbar puncture revealed the cerebrospinal fluid pressure to be 144 mm. of water. On removal of 10 cc. of crystal clear fluid the pressure was 120 mm. of water. The Ayala index was 1.4. The total protein content was 132 mg. per cent.

*Course.* The patient left the hospital to complete some arrangements before undergoing operation. Twelve hours later she returned to the hospital complaining of extreme dizziness. Her speech was thick and she had not voided since the night before. The pulse was weak and irregular. She died within an hour after her readmission of respiratory failure.

*Necropsy findings. Gross.* The brain was of average size and weight, with normal convoluted pattern (fig. 1). A well defined *conus cerebellaris* was present. A tumor, meas-

uring 3 cm. in its long diameter and 1.5 cm. in depth distorted the brain stem. It flattened the upper two-thirds of the medulla and displaced it to the left, and displaced the pons to the left and upward. The ventral surface of the tumor was slightly concave; this surface was rough where the dura had been stripped from its surface. The dorsal surface of the tumor made a depression in the brain stem. It was convex, nodular, and covered by a smooth membrane which was attached to the medulla and pons by numerous small vessels

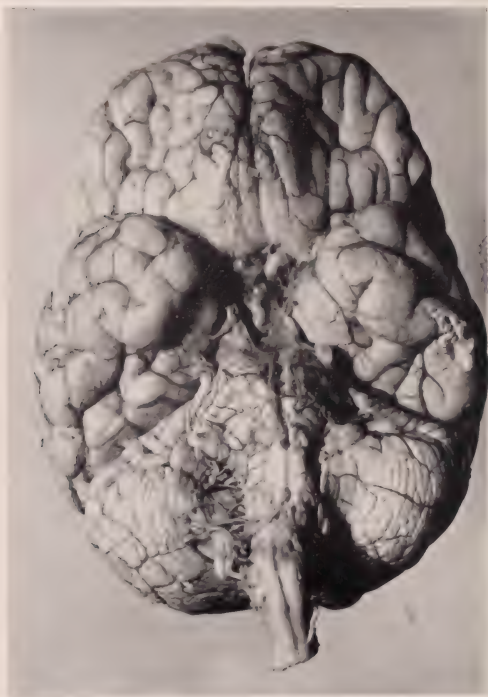


FIG. 2. *Case 1*, gross appearance of the base of the brain after removal of the tumor. Note the deep concave depression and distortion of the pyramids, after the tumor was removed.

and rootlets of pia. At the upper end of the depression in the brain stem the seventh and eighth nerves were found greatly flattened. The ninth and tenth nerves were also flattened and thinned by pressure of the mass.

On the removal of the tumor (fig. 2), a fairly deep, concave depression was found, the floor of which was smooth and covered with pia-arachnoid. There was marked distortion of the pyramids. They were displaced to the left. The right pyramid was markedly thinned

and the adjacent olive could scarcely be recognized. An occasional rootlet between the olive and pyramid was recognized. Otherwise there was no sign of the hypoglossus, and the spinal accessory could not be identified.

*Microscopic observations.* Hematoxylin and eosin stain of sections through the tumor showed a large amount of connective tissues distributed as interlacing strands and septa (fig. 3). Moderate numbers of typical fibroblast cells were present in the connective tissue stroma. The connective tissue enclosed well-defined cells with moderate amounts of cytoplasm and oval or elongated, darkly-staining nuclei. The cells varied in size and shape but were arranged in definite patterns of winding columns, clumps and rosettes. Many of the columns and clumps of cells had well-defined central channels.

The cellular pattern of the tumor is clearly one of embryonal capillary growth and proliferation. The tumor was reported by Dr. J. H. Globus as an example of a pial meningioma.

*Comment.* In the foregoing case the first objective neurological finding was the involvement of the hypoglossal nerve, consisting of atrophy and fibrillations of the right half of the tongue and deviation of the tongue to the right. In view of the affliction of the lower neuron a tentative diagnosis of amyotrophic lateral sclerosis was made by her physician. This diagnosis was only abandoned three years later when unsteadiness of gait made its appearance.

Like two other cases already cited, one of the first complaints was of cough and tickling sensations in the throat. Headache occurred very early and became progressively worse. The rigid position in which she maintained her head and her resistance to change of position was much like that frequently encountered not only in tumors of the posterior fossa, but also in those of the foramen magnum and of the upper cervical cord (5 and 6). This was found in two of the four cases of intracranial neuroma of the hypoglossal nerve previously referred to. Bailey, Buchanan and Bucy (7) state that stiffness of the neck in posterior fossa tumors means that the tumor has extended into the foramen magnum or forced the cerebellar tonsils deeply into it. Wherefore, movements of the head or neck cause pain by pressure or tension on the meninges and upper cervical roots.

*Case 2. History.* (Adm. #539613, P.M. #13245) The patient, a married woman, aged 40 years, was apparently well until one year before entering the hospital when, following exposure to a drenching rain, she began to have pain. The pain was pressing in character, affecting the left side of the vertex, occurred almost every night, and was not relieved by medication but was somewhat alleviated when she assumed an upright position. Four months later, she became aware of a sense of "heaviness" in the tongue which interfered somewhat with talking and swallowing. In another six months the head pain had shifted to the left ear without causing impairment of hearing or any other auditory dysfunction. At about the same time, her voice became weak and brassy. Nine days before entering the hospital (about a year from the onset of her symptoms), she felt nauseated and perspired profusely. Shortly thereafter she fainted, remaining unconscious for about one minute. She entered the hospital on July 16, 1945.

*Examination.* The positive neurological findings included: slight facial asymmetry with some weakness of the left side of the face only at rest; absent gag reflex; the left soft palate was paretic; there were dysphagia and dysphonia; there was paralysis of the left recurrent laryngeal nerve; a nodule which was thought to be an enlarged lymph node was palpable in the right side of the neck; the left sternocleidomastoid and trapezius muscles exhibited some atrophy; there was deviation of the tongue to the left with atrophy of its left side; the vestibular and audiometric tests were negative.

*Laboratory data.* A lumbar puncture yielded clear cerebrospinal fluid under an initial



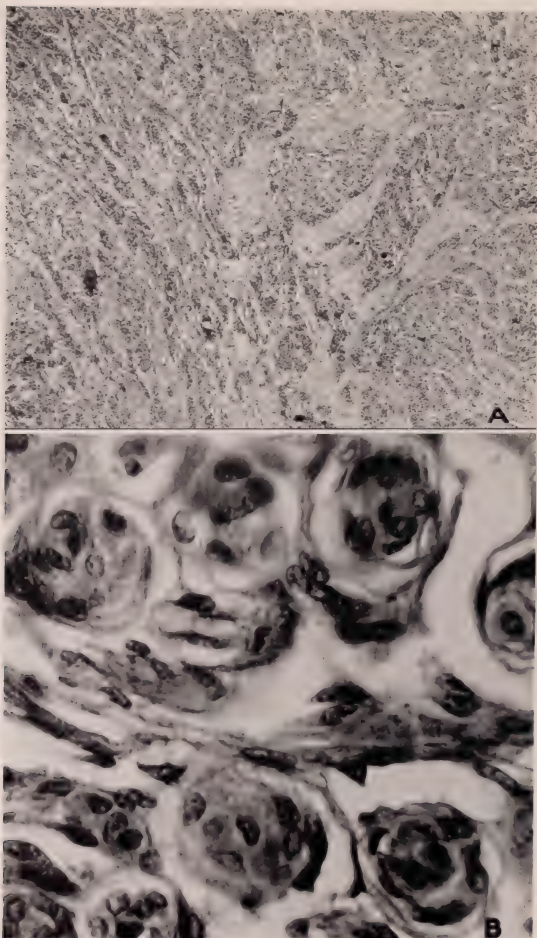


FIG. 3. *Case 1*, section of the tumor showing large amounts of connective tissue distributed as interlacing strands enclosing cell groups which are arranged in patterns of widening columns, clumps and rosettes. Photomicrograph; hematoxylin and eosin stain.

pressure of 150 mm. of water, and a final pressure of 130 mm. of water. The total protein content was 104 mg. per cent.

*X-ray examination* of the skull (fig. 4) revealed "a density in the base of the skull on the left side in the region of the anterior half of the petrous pyramid."

*Course.* The neurological findings indicated involvement of the ninth, tenth, eleventh and twelfth nerves on the left side without apparent implication of the long ascending or descending tracts. A meningioma in the vicinity of the jugular foramen was considered as the most probable lesion. One observer, who noted many naevi and fibromata of the pa-



FIG. 4. Case 2, x-ray of base of skull

tient's skin, suggested the likelihood of a neurofibroma arising from the hypoglossal nerve. The location of the neoplasm was such as to make surgical approach very hazardous and, therefore, surgical intervention was not urged.

The patient left the hospital twelve days after admission (July 28, 1945), and for several weeks her condition remained unchanged. As she became subject to increased difficulty in breathing and swallowing and displayed increasing general weakness, she re-entered the hospital (September 21, 1945). At this time she showed nystagmus on lateral gaze with

definite involvement of the left seventh, ninth, tenth, eleventh and twelfth cranial nerves. There was no papilledema nor any other evidence of increased intracranial pressure. Again she exhibited no involvement of the long tracts. She soon began to complain of tinnitus on the left side and displayed narrowing of the left palpebral fissure, hypalgesia of the left cornea and some ataxia in the left upper extremity. An extra-medullary tumor in the posterior fossa still seemed the most likely lesion but it was thought to be malignant. The question of surgical intervention was again raised but was considered too dangerous and of too little promise to be undertaken. Radiotherapy was therefore instituted. Her condition, however, remained critical. Her airway required clearing by suction and, in spite of the administration of oxygen and penicillin, atelectatic pneumonia of the right lower lobe developed. At the end of three weeks of uninterrupted decline, she suddenly died with signs of respiratory paralysis.



FIG. 5. Case 2, gross appearance of the base of the brain

*Necropsy findings. Gross.* The brain was of average size (fig. 5). The meninges were smooth and glistening. The cortical markings were normal and there was no evidence to indicate that increased intracranial tension had been present. A tumor mass was found at the base of the brain on the left side. This was thickest over the left half of the medulla, thinned out as it extended to the left over the anterior portion of the ventral cerebellar surface. The medulla bulged to the right, the pons was displaced upward. The left vertebral artery was entirely covered by the tumor mass. The seventh and eighth nerves were readily identified, they were moderately compressed but otherwise not damaged. The ninth, tenth and twelfth nerves could not be identified. Part of the eleventh nerve could be seen emerging from the substance of the tumor mass.

The brain, when sectioned, showed moderate internal hydrocephalus with the right lateral ventricle slightly larger than the left. The left side of the fourth ventricle was

deformed by pressure of the tumor. The tumor was adherent to the undersurface of the left cerebellar hemisphere; its medial one-third infiltrated the left half of the medulla. The entire length of the tegmentum was almost completely replaced by the tumor which measured 3.5 cm. in its largest diameter. The right half of the medulla was compressed and appeared enlarged. The cut surface of the tumor was rough, granular, reddish gray-brown color and sprinkled with dark brown areas which in some places had a hemorrhagic appearance.

*Microscopic observations.* Sections of tumor tissue (fig. 6), stained with hematoxylin and eosin and with the Nissl method, disclosed large, irregularly convoluted, sinusoidal channels, containing blood and separated from each other by alternately, rather cellular and loosely reticulated tissue. Collections of a serous fluid appeared both extra- and intravascularly. The cells of the intervacular tissue contained oval or round, darkly staining

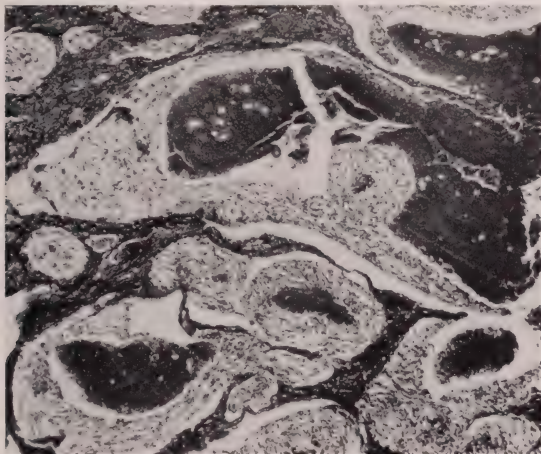


FIG. 6. Case 2, section of the tumor showing large, irregular, convoluted sinusoidal channels containing blood and separated from each other by cellular and loose-reticular tissue. Photomicrograph; hematoxylin and eosin stain.

nuclei and a moderate amount of cytoplasm. Some of the nuclei were unusually large. Where the cells were especially dense, they assumed stream-like formations. The vascular channels were lined by a thin layer of large, pink cells with distinctly outlined, oval nuclei containing small amounts of finely granular chromatin and with an abundance of cytoplasm which had a syncytial character. Occasionally, the vessel wall seemed to have coalesced and formed a broad band. Mallory stain disclosed a moderate amount of connective tissue in the linings of the vascular channels. A few, well-formed, thick-walled blood vessels were encountered.

The tumor was reported by Dr. J. H. Globus as an hemangioma (cavernomatous pial meningioma).

*Comment.* In this case, too, involvement of the tongue and aggravation of head pain by change of position of the head were early manifestations. The subsequent implication of the ninth, tenth and eleventh cranial nerves consti-



tuted a symptom complex which could have been explained by an extracranial lesion in the retroparotid space. However, the head pain accompanied by nystagmus and ataxia definitely placed the lesion within the cranial cavity.

The final diagnosis of the tumor as an hemangioma is of special significance, since multiple naevi and generalized neurofibromatosis were observed during the clinical course. Not without interest is the fact that of the six cases of neurofibroma of the hypoglossus generalized neurofibromatosis was found in two.

*Case of Martel, Subirana and Guillaume (8).* In this instance coughing and a ticklish sensation in the throat was an early symptom. It was followed by headache which was characteristically aggravated by change of position of the head and was soon followed by the development of papilledema, deviation of the tongue to the left, peripheral left facial weakness and paresis of the left soft palate. At operation a tumor was found attached to the left hypoglossal canal and to the left side of the medulla.

*Case of Bailey, Buchanan and Bucy (7)* was one in which a neurinoma of the hypoglossal nerve occurred as part of a generalized neurofibromatosis. It was discovered in a girl, aged 16 years. She was operated on for a glioma of the optic chiasm four years earlier. She developed pain behind the right ear and atrophy of the right side of the tongue. This was followed by involvement of the right ninth and tenth cranial nerves, weakness of the right arm and leg and unsteadiness of gait. She reacted very poorly during an attempted operation, and died three days later.

At autopsy innumerable fibromata were found throughout the body, also a spongioblastoma of the optic chiasm, an astrocytoma of the cerebellum and several gliomatous nodules in the cerebral and cerebellar cortex. "In the angle between the bulb, pons and cerebellum on the right side there was a firm, nodular tumor 3 cm. in diameter. It appeared to rise from the twelfth cranial nerve, and there was an extension of the tumor through the canalis hypoglossi. . . . The tumor indented the bulb deeply, and to a lesser extent the cerebellum and pons. . . . On the right side the seventh and eighth nerves were elongated because of distortion of the tumor of the twelfth nerve, but were otherwise normal. . . . The right twelfth nerve could not be identified, but the tumor projected through the canalis hypoglossi."

*Haase's case 1.* A woman, aged 52 years, developed headache and stiffness of the neck. It was soon followed by deviation of the tongue to the left and some facial asymmetry. Somewhat later she manifested sensory impairment to touch and pin prick on the right side of the face, weakness of the right sternomastoid and trapezius muscles, paresthesia, impairment of position and vibration sense and of stereognosis in the right arm and weakness in the right leg. Shortly after admission the patient developed bronchopneumonia and died.

At necropsy "a tumor was found covered by the medulla oblongata and its nerves which were compressed between the right margin of the foramen and the tumor mass. The latter had invaded the occipital bone and extended laterally to within 0.5 cm. of the internal acoustic meatus. The seventh and eighth cranial nerves on the left side were free of the tumor but the ninth, tenth and eleventh nerves were elongated and compressed. The left hypoglossal nerve terminated in a tab of tissue continuous with the neoplasm." The tumor was diagnosed as a neurofibroma.

*Haase's case 2.* A woman, aged 43 years, began to experience a tickling sensation in the throat, cough and developed weakness of the right side of the tongue. This was followed by dysphagia, slurred speech, attacks of dizziness and pain in the left "suboccipital" area. She vomited frequently and shortly afterward she complained of numbness of the left hand and foot and of unsteadiness of gait. The ninth, tenth, eleventh and twelfth cranial nerves were found to be affected. An x-ray examination disclosed erosion of the occipital bone in the region of the hypoglossal canal.

At operation "a yellowish tumor was seen displacing the bulb backward and to the right. The eleventh cranial nerve was stretched over its postero-medial surface. On its medial



surface several nervous filaments obviously rootlets of the twelfth cranial nerve could be seen. . . . When this tumor had been removed another could be seen anterior to it."

The patient died two days postoperatively of respiratory failure. No autopsy was reported by the author in this case.

In view of the rarity of the tumors under discussion and since they present a constellation of signs and symptoms which serve as excellent leads for the recognition of the nature and seat of such lesions we thought it desirable to add two new instances.

#### SUMMARY

Intracranial tumors of the hypoglossal nerve are characterized by the appearance of some early subjective disturbances of the tongue preceding the ultimate development of atrophy, fibrillations and deviation of the tongue. The clinical course in such tumors is marked by frequent implication of other cranial nerves, particularly of the 9th, 10th and 11th, and invariably by the appearance of signs of increased intracranial pressure and/or brain stem involvement. They may show roentgenologic changes in the base of the skull, such as were found in two of the cases. In addition they may cause any or all of the other well-known signs and symptoms of other posterior fossa, foramen magnum and upper cervical cord neoplasms.

In all of the reported cases, tumors of the hypoglossal nerve were found to be either neurinoma or hemangiomatous neoplasms, and in a high proportion they were found associated with generalized neurofibromatosis and multiple naevi.

Two new cases of intracranial tumors of the hypoglossal nerve have been reported and the features of such tumors discussed.

The authors wish to express their gratitude and appreciation to Dr. Joseph H. Globus without whose kindly criticism and unfailing assistance this paper could not have been written.

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## SPREAD OF INFECTION FROM FACE AND JAWS

### ANATOMIC CONSIDERATIONS

HARRY H. SHAPIRO, D.M.D.

*Department of Anatomy, College of Physicians and Surgeons, Columbia University*

*Introduction.* The blood stream, the lymphatics and spaces established between layers of fascia supply anatomic pathways for the spread of infection. As an example of the significance of the venous drainage in the spread of infection, one may consider the angular, facial and ophthalmic veins. The absence of valves in these vessels accounts for the manner in which septic thrombi can be transported through these venous channels to the cavernous sinus, causing sinus thrombosis or general infection of the blood.

The lymphatic system supplements the venous drainage of the body. The filtering out of foreign bodies which may have invaded the tissues takes place in the lymph nodes or glands which are located along the course of the lymphatic vessels. The slow passage of lymph through the nodes permits the absorption of toxic substances, causing swelling of the nodes, making them palpable, and therefore of diagnostic value.

Infection in the neck is commonly known to have its origin in the head, septic material from sinuses, tonsils, teeth or jaws being carried to lymph nodes along the carotid sheath. Because structures located anterior to the cervical vertebrae are most often involved in secondary infection in the neck, the prevertebral region is of special significance when dealing with morbid conditions.

*Fascial layers.* Continuous layers of connective tissue (the fasciae) sheath, bind together or support internal structures. These fasciae vary in thickness and strength, and are commonly classified as superficial and deep layers.

The superficial fascia (*tela subcutanea*) lies immediately under the skin and serves as a connection between the skin and the deep fasciae. Within its meshes are nerves, vessels, lymphatics, and a varying amount of fat deposits. In the region of the face, this layer contains the muscles of expression; in the neck, the platysma muscle is contained within it. This most superficial of the fasciae is the site of superficial cellulitis, which may extend from the head to the neck and torso, accumulations of infected material gathering in the cervical region either superficial to or deep to the platysma muscle. The relation of the platysma to the superficial fascia and external layer of the deep fascia may be seen in the transverse section of the neck shown in Figure 2, \* 24.

The deep fascia, differentiated and specialized, supports groups of muscles, investing each of them with a protective covering, and encapsulates organs and glands, binding them more or less firmly together.

The outermost layer of the deep fascia, known as the external cervical fascia, is located beneath the *tela subcutanea*. All the structures of the neck are enveloped in this snugly adapted collar of tissue (fig. 2, \* 15, 23, 26, 28), thus forming a fascia-enclosed compartment of the entire neck, excepting those tissues and

structures which occupy the interval between the external layer of the deep fascia and the skin. Fascial processes or alae extend inward from the external layer



FIG. 1. Fasciae of the head and neck (after Eisler). From Morris' Human Anatomy.

of fascia and connect it with the deeper layers of fascia which enclose groups of muscles, glands, vessels and nerves.

Reference to Figure 1 will serve to demonstrate the superficial layer of the deep fascia (external cervical fascia). In this figure, the overlying tissues and structures, the skin, the superficial fascia (*tela subcutanea*) and platysma muscle

have been dissected away. Portions of the external cervical fascial envelope have been opened to show deeper fasciae; the external jugular vein, the anterior jugular vein and the median vein of the neck are shown penetrating and lying on the external layer of fascia (fig. 1, ¶6, 7, 8); part of the sternocleidomastoid muscle, submaxillary and parotid glands have also been removed. Figure 1, ¶3 shows the cut end of the sternocleidomastoid muscle, and ¶1 and 2 in this same figure indicate the areas from which the submaxillary and parotid glands have been dissected.

The external cervical fascia not only encloses the structures of the neck but in its upward extension on the face, invests the parotid gland, covers the masseter muscle, attaches to the zygoma and is continued above as the outer layer of the temporal fascia. In the neck this layer of the fascia splits to invest the trapezius muscle, extends across the posterior triangle of the neck, divides to enclose the sternocleidomastoid muscle and is continued to the mid-line where it joins the external cervical fascia of the opposite side. It is attached to the spines of the cervical vertebrae posteriorly and to the clavicle inferiorly. The hyoid bone, to which the fascia is attached anteriorly, separates the upper, submaxillary portion from the infrahyoid division. This latter portion of the fascial layer extends to the sternum where it splits and is attached to the anterior and posterior borders of the manubrium, thus forming the space of Burns (fig. 1, ¶5). The suprahyoid portion of the external fascia is attached to the lower border of the mandible, extends across the submaxillary and submental areas, joins the fascial coverings of the digastric and stylohyoid muscles and encloses the submaxillary gland.

A middle cervical (pretracheal) layer of fascia consists of outer and inner layers. The outer layer encloses the sternohyoid (fig. 2, ¶8) and omohyoid muscles. The inner layer, thinner and weaker than the outer, invests the thyrohyoid and sternothyroid muscles (fig. 2, ¶12). The outer and inner layers fuse in their lateral extension and are attached to the carotid sheath which encloses the carotid artery, the vagus nerve and the internal jugular vein (fig. 2, ¶19, 21, 22). The middle cervical fascia is attached to the hyoid bone above, and to the sternum and clavicle below, joining the external cervical fascia and the carotid sheath beneath the sternocleidomastoid muscle (fig. 2, ¶23).

Another layer of the deep fascia, the visceral fascia, encloses the thyroid gland, the trachea and the esophagus (fig. 2, ¶10, 13, 14). This layer forms a compartment in the neck between the middle cervical and prevertebral fascia and extends from the base of the skull to the thorax.

An additional layer of the deep cervical fascia, the alar fascia, described by Grodinsky and Holyoke, is situated between the prevertebral fascia and the fascia which covers the pharynx, the esophagus and the visceral structures. This layer is continuous with the prevertebral fascia at the tips of the transverse processes of the vertebrae, where both layers are attached; the lateral extension of the alar fascia forms the carotid sheath.

The deep layer of the deep cervical fascia, the prevertebral fascia, covers the bodies of the cervical vertebrae, the longus colli and the scalenus muscles (fig. 2, ¶4, 5, 9), and other deep muscles of the posterior neck region.



*Fascial spaces.* Fascial spaces are formed in potential areas between layers of fascia. When invaded by infection, loose connective tissue normally located between the fascial layers breaks down and the spaces thus established are replaced by infected material. Communications between fascial spaces of the head and neck have been demonstrated by Grodinsky and Holyoke who studied seventy-five adult cadavers and five full-term fetuses by dissection, injection and section methods.

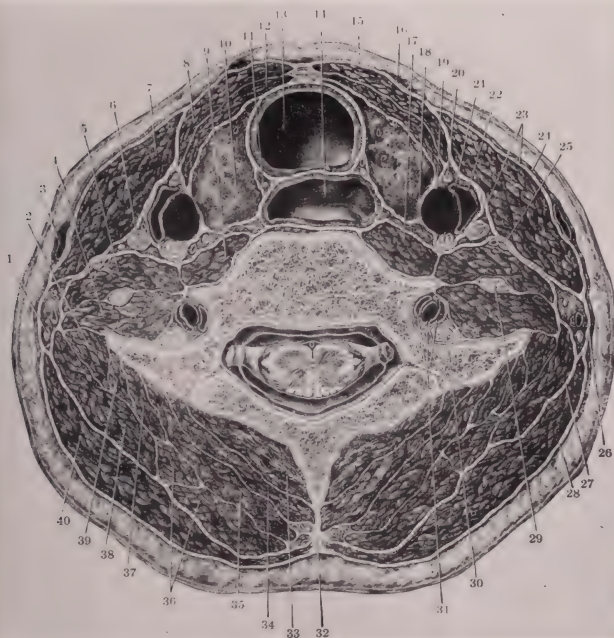


FIG. 2. Transverse section of the neck (Deaver). From Morris' Human Anatomy.

The layer of the deep cervical fascia which covers the masseter muscle externally (fig. 1) and the internal pterygoid muscles internally, forms the walls of the masticator space. These muscles and the ramus of the mandible are contained within the space, which communicates above with the temporal space, beneath the deep temporal fascia. Infection in the masticator space may spread to the parotid, the temporal, the lateral pharyngeal or the submandibular spaces.

The parotid space (fig. 1, #2) is enclosed by the superficial layer of the deep fascia, and includes within its contents the parotid gland, the external carotid



artery and the posterior facial vein. Infection in this space may involve the substance of the parotid gland, or spreading inward, may pass to the masticator, the lateral pharyngeal or the submandibular space. Because the capsule surrounding the parotid gland is of greater strength externally, the spread of infection is usually limited in an outward direction, but passes readily inward through the weaker fascial layer beneath the gland. The intercommunication of fascial sheaths may be exemplified by the parotid fascia, its inelastic outer covering accounting in part for the pressure and the consequent pain experienced when the gland is swollen, as in parotitis.

The lateral pharyngeal space is difficult to visualize; a careful consideration of its boundaries may be of assistance in localizing the area. The pharynx forms the medial wall; the styloid muscles and carotid sheath limit the space posteriorly; the parotid gland forms the posterior lateral boundary; the pterygoid muscles, the mandible and the masseter muscle limit the anterior lateral wall; the pterygomandibular raphe establishes the anterior boundary. It will be recalled that the pterygomandibular raphe serves as the line of connection between the buccinator muscle and the superior pharyngeal constrictor muscle. This thin slip of fascia extends from the pterygoid hamulus above to the buccinator crest of the mandible below; the upper attachment of the raphe may thus be localized by palpating the pterygoid hamulus in the roof of the mouth, thereby assisting one to locate the anterior limit of the lateral pharyngeal space, for the area lies behind the pterygomandibular raphe.

The space extends, above, to the base of the skull and is limited below by the attachment of the submaxillary fascia to the coverings of the stylohyoid muscle and the posterior belly of the digastric muscle. Free communication exists between the lateral pharyngeal space and the submandibular space; infection may also spread to the retropharyngeal area.

The submandibular space, a term coined by Grodinsky and Holyoke, includes "the regions of the submental and submaxillary triangles lying between the mucous membrane of the floor of the mouth and the superficial layer of deep fascia over these regions." The submaxillary and sublingual glands and a group of muscles which include the genioglossus, geniohyoid, mylohyoid and anterior belly of the digastric are enclosed in the submandibular space; the hyoglossus and superior pharyngeal constrictor muscles form the floor of the space. The fascial coverings of these various structures form a group of potential spaces which communicate with each other.

Infection in the submandibular space may spread across the floor of the mouth, into the deep submaxillary area, the lateral pharyngeal space, the retropharyngeal space, and thus to the superior and posterior mediastinum. Accumulations within the floor of the mouth may extend posteriorly to the faucial pillars, the pharynx and the larynx, producing submucous swellings, as in Ludwig's angina, which may result in asphyxiation. Extension of infection from the submandibular space may also spread to the superficial layer of fascia of the head and neck, or along deeper fascial envelopes in the neck.

The retropharyngeal space is limited behind by the prevertebral fascia which covers the cervical vertebrae, the longus colli muscles (fig. 2, ¶9), the scalenus muscles (fig. 2, ¶4, 5), and other deep muscles of the posterior neck region. This space, which extends from the base of the skull to the posterior mediastinum, is referred to as the "danger space." Infection in the floor of the mouth, or retropharyngeal abscess, carried to the pharyngeal area by veins or lymphatics, may reach the mediastinum by way of this route.

#### SUMMARY

Anatomic considerations related to the spread of infection from the face and jaws are briefly stated. Superficial and deep layers of the fasciae and fascial spaces are discussed. The reader is referred to references listed below for more detailed accounts of the anatomy and aspects of special surgical significance.

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## PHLEGMON OF THE FLOOR OF THE MOUTH

(LUDWIG'S ANGINA)

GABRIEL P. SELEY, M.D., D.O.S., F.A.C.S.<sup>1</sup>

The term Ludwig's Angina has been used for many years to describe a particular type of infection of the floor of the mouth. Actually the first description of the disease was by Gensoul of Lyons, France in 1830. By definition angina (Latin *angere*: to choke) refers to any disease or symptom characterized by spasmodic suffocative attacks especially a disease of the pharynx or fauces exhibiting such attacks. Since the disease is not an angina and was not first described by Ludwig, the term "phlegmon of the floor of the mouth" should be substituted for the term Ludwig's Angina.

*Etiology.* The infection usually arises from an infected tooth situated in the lower molar region and rapidly spreads to the cellular tissues of the floor of the mouth. This cellulitis then extends in a plane deep to the geniohyoid and mylohyoid muscles. It may and does spread to the contra-lateral side of the neck into the opposite sub-mylohyoid space. In the series of cases studied infection followed extraction or tooth ache (as a result of dental infection) in the majority of patients. In one case there was simply poor oral hygiene and in another the direct trauma of a dental burr to the floor of the mouth was the exciting cause. In only one instance did the phlegmon follow extraction of an upper molar. The indiscriminate use of local infiltration anesthesia in and about an infected tooth may be a contributory factor in the etiology of this disease.

*Pathology and bacteriology.* The infection is acute and fulminating in most instances. Although it starts as a cellulitis it rapidly progresses to form a phlegmon and in turn very rapidly become purulent. In one case in which the trauma of dental burr was the cause the signs and symptoms were mild and cure occurred with conservative therapy without pus formation. In all the other cases with classical signs and symptoms pus was present.

Bacteriological studies have not been complete. In those cases in which cultures were taken a variety of micro-organisms were grown out including anaerobic non-hemolytic streptococcus, anaerobic staphylococcus parvalus, streptococcus hemolyticus beta, staphylococcus albus beta and streptococcus viridans. In most, if not all, of the cases the infection is mixed—aerobic and anaerobic. The offending micro-organisms are those present in the mouth and the causative agents of dental sepsis. The presence of foul pus in the majority of the cases and the presence of gas in the tissues at operation and on pre-operative roentgenograms in some instances further corroborates the impression that there is an anaerobic factor in most of the cases. Thus with rare exceptions we are dealing with a phlegmon due to anaerobic and aerobic micro-organisms which goes on to suppuration in a relatively short time. The pus which is usually foul is locked up under tension and the resultant edema of the surrounding tissues is marked.

<sup>1</sup> Adjunct surgeon, The Mount Sinai Hospital, New York.

Unless the pus is promptly drained death will ensue. The infection may travel down the tissue planes into the mediastinum producing mediastinitis, empyema and pericarditis. Edema of the glottis may cause death by suffocation unless drainage of the infection is performed and in some instances tracheotomy may also be indicated in addition to drainage. In some cases a gangrenous myositis may result requiring excision of muscle bundles.

Pathological examinations of the submaxillary salivary glands removed at operation revealed some normal glands and evidence of acute or chronic inflammation in others. There was no uniformity about the findings in these glands.

*Symptomatology.* The signs and symptoms of this disease are directly referable to the pathology. Elevation of the tongue and edema of the floor of the mouth are caused by the presence of pus under tension between the mylohyoid muscle and the mucous membrane of the mouth. Brawny induration of the submandibular region without fluctuation is also caused by the presence of pus deep to the cervical fascia and mylohyoid muscle. Fever, chills and toxemia are a result of the presence of foul pus under tension. Difficulty in swallowing, breathing and talking all are due to edema of the structures surrounding the pharynx and glottis. Trismus is a result of severe infection in the mouth and may be present in any case of dental sepsis.

*Diagnosis.* A history of extraction or dental sepsis involving a tooth or teeth of the lower molar region, followed by pain, swelling, trismus, fever (with or without chill), rapid pulse, toxemia, elevation of the tongue, brawny induration of the sub-mandibular region associated with difficulty in talking, swallowing and breathing constitute the classical signs and symptoms of phlegmon of the floor of the mouth. Roentgenograms of the neck may show air in the tissue spaces. A pericoronal abscess about an unerupted third molar or an acute alveolar abscess may produce trismus, swelling of the jaw, fever and pain. However when edema of the floor of the mouth, elevation of the tongue and brawny induration of the submandibular region are present the process of necessity is a phlegmon of the floor of the mouth.

*Management.* Phlegmon of the floor of the mouth is a serious disease and the mortality may be as high as 40 per cent. Death is caused by suffocation or spreading infection as described under pathology. The avoidance of undue trauma in tooth extractions and the limited use of local infiltration anesthesia in infected cases may be of value in preventing this serious disease.

Once the diagnosis is made a decision as to the correct therapy must be arrived at without delay. The rapid spread of the infection and rapidly changing clinical picture allows no time for deliberation.

The use of chemotherapy is this disease has been widespread and there are many reports in the literature. The various sulfonamides have been tried and it is the consensus of opinion that they are of little value. Penicillin is now being used and there have been a number of what appear to be favorable reports. The great difficulty in evaluating these results lies in the fact that some of the cases do not satisfy the rigid criteria for diagnosis and in others surgery was em-

ployed in conjunction with penicillin. In three personal cases in which penicillin was used two were uninfluenced and in the other the patient felt better and was less toxic but the infection continued to spread and necessitated very wide surgical drainage. This latter patient was an Italian co-belligerent operated upon at the 3rd General Hospital, U. S. Army, in France. He required excision of both submaxillary glands, division of the mylohyoid and geniohyoid muscles and excision of considerable musculature for gangrenous myositis. The penicillin merely masked the true progress of the disease and his recovery was attributable to radical surgery. Penicillin is of value both pre- and postoperatively in controlling some of the micro-organisms responsible for the disease.

However if chemotherapy is to be tried without surgery it can only be safely employed in early mild cases. The patient must be constantly observed and evaluated and if marked improvement does not occur within a relatively short time (8-12 hours) surgery should be performed. The improvement should be objective using the edema of the floor of the mouth, the sub-mandibular induration, the temperature level and pulse rate as guides. If chemotherapy is to be of value it must be used before pus is formed, while the infection is in the cellulitic state, and in those cases in which the micro-organisms happen to be penicillin sensitive. Up to the present I have not seen a case in which penicillin prevented the infection from progressing to the phlegmonous and purulent state. One must constantly bear in mind the fact that pus formation is early and evacuation of the pus is necessary for cure.

Intra-oral incision was performed in several of the cases and in only one was there evidence that the course of the disease was favourably influenced by this procedure. This was a mild case and only a few drops of pus were obtained at operation.

Since the infection is deep to the mylohyoid muscle and deep cervical fascia one cannot wait for the pus to present itself superficially. Fluctuation in the neck does not occur.

Spontaneous evacuation of pus into the mouth took place in five cases all of whom recovered. In two of these unsuccessful external drainage had been performed prior to the intra-oral rupture. In two cases intra-oral revision was performed to facilitate the intra-oral drainage which took place spontaneously. One case went on to cure without surgery. These again illustrate that evacuation of the pus is necessary for cure. External operation should be performed under local infiltration anesthesia because of the danger of glottal edema and laryngeal spasm with inhalation or pentothal (intravenous) anesthesia. A tracheotomy set should be ready in the operating room and at the bedside post-operatively. An adequate sub-mandibular incision should be made with exposure of the sub-maxillary salivary gland after the skin platysma and superficial fascia is traversed. Removal of the sub-maxillary gland should be performed if it appears to be obstructing and prevents adequate exposure. In a fair number of cases it was not necessary to remove the gland. Mere removal of the gland is not sufficient. The *sine qua non* of the operation must be the finding of pus and its drainage. If the mylohyoid muscle is traversed



pus under tension (usually foul) will be encountered and the tract will lead up to the floor of the mouth at the site of the offending tooth or tooth socket. The pus may and frequently does traverse the mid-line under the geniohyoid muscle. If it does, counterdrainage by a separate incision on the contralateral side of the neck should be instituted as well as drainage across the mid-line deep to the geniohyoid. If any muscle bundles are severely infected or gangrenous they should be resected. After all the pus is evacuated by the use of suction and gauze sponges, plain (mastoid size) packings should be placed to the depths of the tracts including one to the mucous membrane of the mouth at the site of tooth infection or extraction. A through and through tube drain inserted in the mouth has been advocated but is probably unnecessary if the dissection has been thorough. The packings should be replaced in 24 hours at which time the wound should be irrigated with dilute (5 per cent) hydrogen peroxide solution. Zinc peroxide (as a paste) may be left in the wound to further combat the anerobic infection. Frequent mouth washes with dilute hydrogen peroxide should be instituted immediately after operation. Penicillin (parenterally) which was started pre-operatively should be continued in order to control any residual cellulitis that may be present. Chemotherapy may be discontinued when the wound looks clean and the patient is afebrile. Secondary closure of the wound is unnecessary. Delayed plastic repair may be performed if indicated but only after an interval of at least two months has elapsed to insure the absence of residual infection in and about the wound.

#### SUMMARY AND CONCLUSIONS

1. Phlegmon of the floor of the mouth (Ludwig's Angina) is a serious disease and usually follows dental sepsis.
2. Penicillin therapy by itself should only be used in early mild cases with the patient under careful observation. External surgical drainage should be performed if improvement is not prompt and in severe fulminating cases on admission to the hospital.
3. Surgical drainage should be external (extra-oral) with or without removal of the sub-maxillary salivary gland.
4. Pus (usually foul) under the mylohyoid muscle is a constant finding and adequate drainage is necessary for recovery.

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# SPREAD OF INFECTION FROM THE JAWS TO THE SUBMAXILLARY REGION<sup>1</sup>

## CLINICAL CONSIDERATIONS

LEO STERN, D.D.S.

Definition of the entities variously called submaxillary abscess, phlegmon, cellulitis, or Ludwig's angina remains confused, and considerable disagreement is evident regarding their pathology and treatment. This paper seeks to describe the variations of these diseases and to explain their pathogenesis, differential diagnosis and management.

These infections are of two main varieties, arising from the oral structures and descending to the submaxillary triangle, and sometimes anteriorly or posteriorly to it. In the great majority of cases the condition is a frank abscess associated with zones of cellulitis of little clinical significance. In these, pus burrows through the mandible into the soft tissues beneath, or else superficial lymph nodes become involved and quickly suppurate. The other variety, and far rarer, is essentially a massive, spreading cellulitis of the subjacent connective tissues, in which reservoirs of liquefaction may or may not occur; such suppuration is generally deeply situated and sometimes missed at operation.

The entity first described may accurately be termed submaxillary abscess. The condition classically described by Ludwig is of the second variety, and sometimes occurs, as he stated, without suppuration. This has been verified by careful postmortem examination in three cases observed, and by many other reporters. However in the group most frequently encountered, despite *clinical* signs identical with those described by Ludwig, a deep-seated abscess is generally found.

*Etiologic factors.* Either condition develops from a dental or oral focus in about 95 per cent of cases. The remainder follow residual lymph node involvements of an upper respiratory infection, exanthem or tuberculosis, and occur mostly in young children. Many begin spontaneously after an acute periodontal, periapical or pericoronal infection of a posterior mandibular tooth associated with pericistitis of the lingual aspect of the mandible. A few seem to follow subperiosteal contamination during a local anesthetic injection; these often show an early tender swelling over the inferior dental foramen before submaxillary extension is noted. The largest number of phlegmons however come as a sequel

<sup>1</sup> This article as well as the preceding two relating to the subject of infections of the floor of the mouth and the submaxillary region were presented at the Dental Conference, The Mount Sinai Hospital, on November 20, 1946.

Dr. Harold Neuhof has offered the following remarks as an introduction: It is always heartening to note a symposium in which a single surgical subject is approached from various angles, for a well-rounded view of that subject is apt to be achieved. The present symposium, dealing with a subject calling for elucidation, is decidedly informative and a perusal of the various contributions will in fact provide a well-rounded view of a difficult clinical condition.

to traumatism, accidental or surgical, and particularly, following the removal of an impacted mandibular third molar. In a few of these cases, the patients are diabetic, a few customarily react profoundly to any surgery. The rest, it may be assumed, are subjected to considerable traumatism or are operated on before the dental infection is adequately walled off, or both.

*Mode of spread.* When a superficial dental infection invades the submaxillary space it probably travels along the lingual surface of the mandible. Periapical or deep-seated pus burrows from the medullary bone spaces and may perforate the cortical plate at almost any point. In perforations occurring high, near the alveolar process, a localized subperiosteal abscess is the rule; lower perforations invariably invade the areolar tissue in the deep reaches of the submaxillary space and some degree of cellulitis follows (fig. 1). From this point one or several dispositions occur. (a) The infection is taken up by the afferent lymph vessels

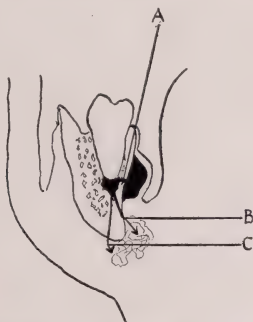


FIG. 1. Diagrammatic cross section in region of lower 3rd molar, showing high perforation of pus (A) to form subperiosteal abscess; (B) and (C) showing lower perforations invading areolar tissue in submandibular space.

and reaches the submaxillary lymph nodes. The nodes may suppurate and involve the submaxillary salivary gland. (b) En route, infection may be picked up by Wharton's duct and carried directly to the gland; the gland becomes inflamed. (c) Concurrently, both pus and cellular inflammation advance along non-resisting paths, namely the circuitous fascial and muscular planes of the region. Cellulitis spreads rapidly and fuses these structures into a solid, indurated mass. As the tough layer of the mylohyoid and associated muscles forms the more slowly yielding barrier, edematous swelling of the floor of the mouth is an early symptom. At this stage, suppuration has not yet taken place; if and when it does, much of it occurs around the capsule of the submaxillary gland, beginning at the posterior margin of the mylohyoid and extending along the deep and superior surfaces of the gland (fig. 2). The salivary gland, with its firm capsule, will often serve as a plug which delays the extension of suppura-

tion superficially. In the great majority of such cases, hot saline irrigations to the floor of the mouth encourages localization and fluctuation, often with spontaneous rupture and prompt improvement. In others, providing the mouth can be opened, incision, with insinuation of a blunt instrument along the deep (inner) surface of the gland, evacuates pus. After resolution, the submaxillary gland seems to function normally and the infection does not recur if the primary focus is eliminated.

*Differential signs.* Although the clinical symptoms of abscess and phlegmon occasionally overlap to a confusing degree, as a rule they are easily differentiated.

In submaxillary abscess there is unilateral soft swelling, redness, and heat. Dysphagia, often associated with otalgia, occurs early. There is no edema of the floor of the mouth or oral fetor, and no fixation of the tongue, and there may be little trismus. Wharton's duct is uninvolved and palpable. The fever is spiking and high, and extraoral fluctuation is noted early.

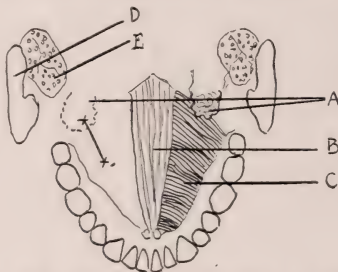


FIG. 2. Diagram of floor of mouth, showing positions of (A) extension of submaxillary sgland, (B) geniohyoid, (C) mylohyoid, (D) ascending ramus, (E) internal pterygoid. 'X-X' shows site of intra-oral incision to expose deep and superior aspects of submaxillary gland.'

In submaxillary phlegmon the swelling is hard and unyielding, far less prominent than in abscess, but spreading laterally more rapidly. The skin is more cyanotic than red. Trismus is generally marked, and edema of the floor of the mouth with lateral displacement of the tongue is one of the most constant presenting signs. Dysphagia occurs later, often with signs of respiratory difficulty, and the breath is fetid. The patient is very ill but the fever generally is not high at first, and probably owes its later rise to a deep-seated abscess. Drainage of such an abscess yields putrid pus, which however does not demonstrate much different flora than the more superficial type.

Both infections are usually mixed and generally there are anaerobes in both. Streptococci and staphylococci predominate, but bacteroides, gas bacilli, colon bacilli, hemophilis influenzae, micrococci catarrhalis and fusospirochetes are sometimes recovered. The bacteriology of submaxillary infections however, has not been too carefully investigated and deserves further study.

*Management.* Chemotherapy, consisting in the adult of 6.0 gms. daily of sulfadiazine with 50,000 units of penicillin every three hours intramuscularly, and occasional booster doses of 100,000 units, sometimes controls either type of infection without surgery. Whereas, this has been more frequently observed in the abscess variety, these are so preponderant that it is erroneous to conclude that they are more penicillin-sensitive, until further experience is gained with the phlegmonous type. It happens more often that surgery is required in the management of phlegmon than not, but even then, chemotherapy is an excellent supportive procedure, makes the patient much more comfortable, and probably reduces the incidence of terminal pneumonia, which in the past has been a large mortality factor. At least 200,000 units of penicillin should be given within 30 minutes of operation to control the bacteremia and local extension which follows manipulation.

Large wet dressings on the face and neck and frequent, copious, hot intra-oral irrigations also promote comfort and undoubtedly determine intra-oral fluctuation in many cases. Examination of the urine and blood for sugar should be routine because several patients in our series were diabetic.

If the patient is treated early in the disease, and edema of the floor of the mouth is already noted, an attempt should be made to open the jaws gently and incise the swelling between the alveolus and tongue, posterior to the molar region and mylohyoid muscle, following both the deep, and superior surfaces of the submaxillary gland with careful, blunt dissection (fig. 2).

*General anesthesia is contraindicated* because of the danger of asphyxia and aspiration. Fairly effective local anesthesia is secured by blocking the third division of the fifth nerve near the foramen ovale extra-orally, supplemented by submucous injection along the line of the proposed incision. This combination has the advantage of partly relaxing trismus and of anesthetizing the deeper structures as well as the superficial.

Block anesthesia is also a valuable supplement to extra-oral incision. Submaxillary abscess, operated at the optimum time, presents no difficulty, as the main abscess is encountered superficially, immediately beneath the platysma. But surgical management of phlegmon, as indicated by Seeley in this symposium, often requires painstaking dissection to the deep aspect of the submaxillary gland before pus is encountered. The intra-oral approach, when feasible, is much simpler and quite effective. In those cases where adequate search fails to disclose a suppurating cavity, ventilation and relief of tension may be the only alternatives, by wide exposure and (a) removal of the submaxillary gland; (b) a division of the mylohyoid and anterior digastric muscles, (c) or both.

Postoperative treatment is supportive and antibacterial with strong emphasis on chemotherapy. Ever-present danger of respiratory embarrassment, which may appear suddenly, dictates the advisability of having a tracheotomy set available at all times until swelling is completely reduced. The dental focus should be eliminated after full clinical recovery as neglect of this step sometimes results in recurrence. Osteomyelitis of the mandible is an occasional



complication, and postoperative roentgenograms should be made several weeks after the onset of symptoms so that it will not be overlooked; its treatment is expectant and conservative.

#### CONCLUSIONS

Although their pathogenesis is identical, secondary infections of the submaxillary region may result either in an abscess or a phlegmon. Even the phlegmonous variety is generally, although not constantly, associated with suppuration. Differential diagnosis is generally easy. Either type is often successfully drained intraorally, but the phlegmonous, if fulminating, should be widely opened extraorally. Chemotherapy alone may be curative, but generally must be reinforced by appropriate surgery.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Parasympathomimetic Effect of Aqueous Humor in Human Eyes With or Without Simple Glaucoma.* S. BLOOMFIELD. Proc. Soc. Exper. Biol. & Med., 60: 293, 1945.

Results are presented of the bioassay of aqueous humor from human eyes according to the method Englehart applied to animals. In a series of 10 human eyes with glaucoma, every sample of aqueous humor contained a parasympathomimetic substance which in 2 cases was found to be similar to acetylcholine. In the aqueous humor of 7 human eyes with chronic simple glaucoma, no such parasympathomimetic substance was demonstrated.

*Repository Injection of Penicillin in Water-in-Oil Emulsion. I. Effect on Gonorrhea.* A. COHN, B. A. KORNBLITH, I. GRUNSTEIN, K. J. THOMSON AND J. FREUND. Proc. Soc. Exper. & Med., 59: 145, 1945.

This study was undertaken to determine if penicillin injected intramuscularly is more effective in a water-in-oil emulsion than in aqueous solution. It was hoped that the absorption of penicillin might be prolonged by incorporating it in a water-in-oil emulsion so that the number of injections and perhaps the amount of penicillin could be reduced. Patients with gonococcal infections were chosen for testing the method because clinical manifestations are usually clear cut and cure can be established readily by bacteriologic methods. A single dose of 200,000 Oxford Units can be prepared without laboratory facilities in the following way: 1.4 c.c. of normal saline are drawn into a sterile syringe and ejected into a vial which contains 200,000 Oxford Units of penicillin. To this penicillin solution 3.1 c.c. of an autoclaved mixture containing 11 parts of a lanolin-like substance and 20 parts of peanut oil are added by means of a sterile syringe and a 17 gauge needle. With the needle still inserted through the rubber cap of the vial, the mixture can be readily emulsified by repeated withdrawals and ejections. As soon as the mixture assumes a uniformly creamy, slightly viscid consistency, satisfactory emulsification has occurred and it is ready for intramuscular or subcutaneous injection. (The oily mixture used for emulsification can be obtained commercially under the name of Pendil, Emulgen and Solvecillin.) Gonococcal infections treated with 150,000 Oxford Units in a single injection of the water-in-oil emulsion, proved successful in 98 per cent of the cases thus treated. When the amount was divided into 50,000 Oxford Units in an aqueous solution as a "priming dose" and 100,000 Oxford Units in water-in-oil emulsion and the total amount i.e. 150,000 Oxford Units given at the same time no failures were encountered in a series of 49 consecutive cases.

*The Psychosomatic Approach to Speech Disorders.* E. FROESCHELS. J. Speech Disorder, 10: 221, 1945.

The psychosomatic approach is of great importance in diagnosis as well as in the treatment of cases of speech disturbance. Not only is this true with respect to types of speech disorders which have been customarily regarded as functional or psychogenic, but it appears to be true in large measure also with those disorders associated with anatomic lesions and physiologic deficiencies.

*Principles and Evaluation of the Various Operations for Urinary Incontinence.* J. NOVAK.  
Urol. & Cutan. Rev., 49: 425, 1945.

The operative procedures recommended for the cure of urinary incontinence may be divided into three groups, a. The restoration of the impaired sphincter muscle; these procedures are effective only in mild cases of stress incontinence. b. The angulation and compression of the urethra and the support of the bladder neck by the interposed uterus. This is a very effective incontinence operation which is particularly adequate in post-menopausal cases with prolapse and retroflexion. c. Procedures which tend to raise and support the bladder neck and to replace the impaired and functionless sphincters by other muscular and facial tissue. All these procedures are very effective but more complicated than the forementioned and involve a greater operative risk. The simplest and least dangerous is the bulbo cavernosus-plasty of Montius which is the operation of choice in this group.

## THE WILLIAM HENRY WELCH LECTURES

THE APPLICATION OF ISOTOPE TECHNIQUE TO PROBLEMS  
OF BIOLOGY AND MEDICINE<sup>1</sup>

DAVID RITTENBERG, M.D.

*Associate Professor in Biochemistry, College of Physicians and Surgeons,  
Columbia University*

Ever since the classic experiments of Lavoisier on combustion, it has been clear that the living organism is in some respects a chemical engine which by oxidation of its dietary components produces useful energy. It has the unique property that, at least during the growth period, it can build its own structure from the same dietary materials as it uses for energy production. The elucidation of the chemical reactions which take place prior to the excretion of the atoms of the diet as excretory products has attracted the attention of chemists ever since chemistry became an independent discipline. It is certainly not necessary for me to allude to all the information which was accumulated by studying the gross changes in an animal which resulted from variations of diet or from surgical extirpation of various organs or cell systems or from analysis of animals having a congenital metabolic anomaly. Such data, while of the greatest value, suffered from the fundamental defect of having been obtained on animals existing under abnormal conditions of one kind or another.

The determination of the fate of any dietary component is complicated by the fact that the composition of the diet is quite similar to that of the living cell. The moment the substance enters the cell it mixes with the same substance already present and the investigator loses track of it. All that could be done was to measure the increase of some natural excretory product or to look for an increase of some other substance, either in the cell or in the excreta. From such data only inferences could be drawn which were more or less favorably received depending on the scientific attainments of the investigator.

It was clear that, if a method were developed by means of which a compound could be labelled, the study of the fate of this substance would be greatly simplified. The first practical application of this concept was made by Knoop. He labelled fatty acids by attaching a phenyl group to the terminal methyl group of the fatty acid. From observations of the manner in which the terminal phenyl derivatives of the C<sub>1</sub> to the C<sub>5</sub> fatty acids were treated by the animal, he developed the  $\beta$  oxidation theory. This theory states that the normal fatty acids are oxidized by a mechanism which removes two carbon atoms at a time. While the text books accepted this theory without qualifications, the experimental basis of the  $\beta$  oxidation theory had gaps in it. Indeed, results were obtained with the phenyl substituted fatty acids because their metabolic fate

<sup>1</sup> Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on Friday, February 7th, 1947.

is different from that of the natural fatty acids. While normally the latter are completely oxidized to carbon dioxide and water the complete oxidation of the former is inhibited by the phenyl group so that one can recover from the urine of animals which were fed these compounds either phenylacetic or benzoic acids, depending on whether the side chain had an even or an odd number of carbon atoms.

In 1923, George Hevesy carried out an experiment in which a label was employed which did not change the physical or chemical properties of the substance to be marked. Hevesy had found that radium D, one of the elements formed during the radioactive decay of radium, seemed to be identical with ordinary lead in all of its properties excepting its radioactivity. We now know that Ra D is actually an isotope of lead, i.e. it has the same atomic number as normal lead. It occurred to him that by adding a small amount of radium D to ordinary lead he would form an inseparable mixture whose presence could be recognized by its radioactivity. Since the methods for detection and estimation of radioactivity are more sensitive than chemical methods for the detection of normal lead, he was able to detect this mixture in very small concentration. The problem he next attacked was the transport of lead in plants. He immersed the roots of a plant in a solution containing a small amount of radioactively labelled lead and followed its transport in the stem and leaves by measurement of radioactivity. This experiment aroused but little interest among biologists since they were not greatly interested in lead metabolism.

In 1930, H. C. Urey discovered a heavy isotope of hydrogen, of atomic weight two, which is universally distributed in nature in the proportion of 1 atom of the heavy isotope to 6000 atoms of the light one. Shortly thereafter he developed methods for the concentration of this heavy isotope and proceeded to prepare not only the heavy isotope of hydrogen, but also extracted from natural sources the heavy isotopes of nitrogen, carbon, oxygen and sulfur. During this period the physicists were preparing radioactive isotopes of the elements and at present there are available radioactive isotopes of every element of the periodic table.

In 1934 the late Dr. Schoenheimer and I took up the problem of labeling organic compounds which are naturally present in living cells. We prepared a specimen of stearic acid in which two hydrogen atoms attached to the ninth and tenth carbon atoms were replaced by deuterium atoms. This sample of stearic acid was by no means unphysiological since normal stearic acid contains some molecules having two deuterium atoms; the cell meets these molecules continually and handles them in the same manner as those which contain one or no deuterium atoms. It is true that in the normal stearic acid only about  $\frac{1}{2}$  per cent contains one deuterium atom and that only 0.002 per cent contains two atoms of deuterium, whereas in the compound we fed, every molecule of stearic acid contained two atoms of deuterium. Nevertheless, this is a quantitative difference and not a qualitative one. While the living cell is not sensitive to such changes in isotope concentrations there exist analytical procedures which can detect and quantitatively measure extremely low concentrations so the



heavy isotopes of hydrogen, carbon and nitrogen. For example, the concentration of deuterium in an organic compound can be determined with an error of about one thousandth of one per cent. It is thus possible by isotope analysis to trace an organic compound in its passage through the living cell and detect its conversion into other compounds.

At the period when we had prepared this first labelled organic compound the theory of the separation of the metabolism into endogenous and exogenous systems was universally accepted. It was based on a widely held view, first advanced by Helmholtz, that the living organism was somewhat similar to a steam engine. The diet, which corresponded to the coal introduced in the fire grate of the boiler, was largely oxidized for energy production. This was the exogenous metabolism. A small part of the diet was not oxidized but employed to repair the elements of the metabolic mill which had worn out. On this basis we expected to find after the feeding of the deuterio stearic acid that some 95 per cent would have been oxidized while about 5 per cent would have been deposited in the cells. This, however, was not the case. After feeding a small dose of fatty acid more than 50 per cent could be recovered from the fat of the rat. This result was found even in the case of an animal on a semi-starvation diet. Despite its acute need for energy the rat incorporated half of its dietary fat in its tissues. However, so firmly was the theory entrenched that several years elapsed before the correct conclusions were drawn from these experiments.

The major organic constituents of the living cell, the fats, the proteins and the polysaccharides, are thermodynamically unstable compounds. Under suitable conditions they can each be broken down to their component building blocks, the fatty acids, the amino acids or the monosaccharides. Further, these constituents in the presence of oxygen can be oxidized to  $\text{CO}_2$ , water, and nitrogen. During life we apparently observe the degradation and oxidation of the dietary constituents but not of the cellular material. This phenomenon, the apparent stability of a chemically unstable compound, however, is found not only in the living world but also in the inanimate one. Ammonia has a tendency to decompose into nitrogen and hydrogen but the rate of this reaction is extremely slow. The decomposition occurs only in the presence of suitable catalysts. On the death of an animal the breakdown of its complex structures begins: autolysis sets in. Since, after death, the proper enzymes are present to catalyse these degradative reactions, it was generally believed that during life the same enzymes were in an inactive state and became active only after the death of the animal. All evidence now shows that this is not the case. The proteolytic and hydrolytic enzymes are continuously active in breaking down the proteins, the carbohydrates and lipids at a rapid rate. This erosion of the cell structure is continuously being compensated by a group of synthetic reactions which rebuild the degraded structures. The adult cell maintains itself in a steady state not because of the absence of degradative reactions but because the synthetic and degradative reactions are proceeding at equal rates. The net result appears to be an absence of reactions in the normal state. During life the living cell continuously works to maintain its unstable state; the approach to equilibrium is a sign of death.

The discovery and the description of the dynamic state of the living cell is the major contribution that the isotope technique has made to the field of biology and medicine. I shall attempt to give you some examples.

From the viewpoint of the dynamic state the results obtained after feeding stearic acid to a rat are quite simple to explain. In the rat the cellular lipids are constantly being hydrolysed to fatty acids and glycerol. The dietary fatty acids as they enter the cell merge with the fatty acids formed by breakdown of the cellular lipids. Of this mixture of fatty acids some are oxidized for energy production and others are resynthesized to lipids. The relative proportion of a dietary fatty acid deposited will depend on the relative rate of synthesis of fat to that of the oxidation of fatty acids to carbon dioxide and water.

I shall later discuss in some detail the application of the isotope technique to the field of amino acids and protein metabolism. I shall here present the results which have been obtained on cholesterol. There are three questions which should be answered in the study of any component of the living cell. They are: 1) How fast is it synthesized? 2) From what substances is it manufactured? And 3) what substances are in turn made from it? The isotope technique has offered an answer to each one of these questions.

Since not all the substances a cell requires may be present in the diet it must have mechanisms available to synthesize the required compounds. One of these nonessential compounds is cholesterol. This compound, discovered by Conradi in 1775, has attracted the attention of biologists for many years because of its structural and biochemical relationship to the bile acids, vitamin D, several carcinogenic agents, the cardiac glucosides and the sex hormones. The actual role which it plays in the cell is quite obscure. Neither the mechanism nor the rate at which cholesterol is synthesized in normal animals was known. If heavy water is injected into an animal than all synthetic reactions which occur will take place in a medium of heavy water and the products will contain deuterium atoms attached to carbon atoms. When such experiments were carried out with mice it was found that the deuterium content of the cholesterol rose as shown in figure 1.

After a period of time the isotope concentration in the cholesterol reaches a maximum value. Since the only way in which deuterium can enter this compound is by a synthesis, the curve is a measure of the rate of formation of the cholesterol. From these data we see that after 25 days the isotope concentration in the cholesterol reaches half its maximum value. This indicates that in 25 days half of all the cholesterol in the mouse has been synthesized. Since these animals were in a steady state, i.e., the total amount of cholesterol in their body did not change, we must further conclude that an amount of cholesterol equal to that synthesized has been destroyed. The lipids of the mouse are not only being hydrolysed to their constituent parts but these are being destroyed and reformed from non-fatty acid material.

The isotope technique offers a method by which it is possible to determine whether one compound, A, is converted to another compound, B. If after the feeding of A, labelled isotopically, compound B is found to contain the isotope

label, it may be taken as a demonstration that compound A has been used in the formation of compound B. While this method is quite simple and elegant it does not, of course, offer any help in the choice of compounds to be tested as precursors. Here intuition and some knowledge of organic chemistry are the only useful guide posts.

Dr. K. Bloch and I, after much thought, finally chose some compounds to be tested as possible precursors for cholesterol. One of the acids chosen was acetic acid. The feeding of deuterio acetic acid in rats gives rise to the formation of deuterio cholesterol. From this it may be inferred that the methyl carbon atom of acetic acid is used in the synthesis of cholesterol.

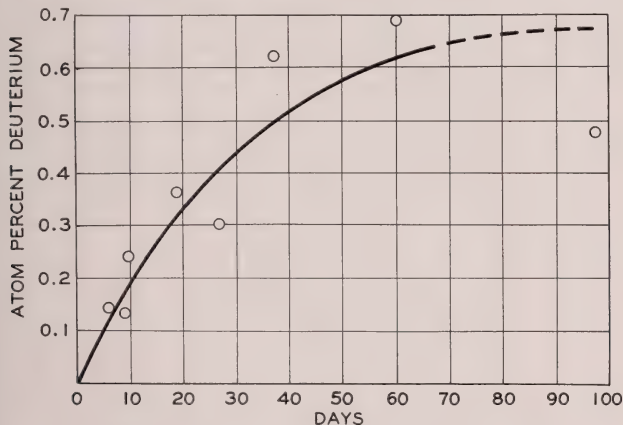


FIG. 1. Deuterium content of cholesterol from mice fed heavy water.

It is obvious that the study of the many reactions which must intervene between the initial compound, acetic acid and cholesterol must be quite complicated and that its study might be simplified if it could be investigated in some system less complex than the intact animal. With Dr. Borek we thus began an investigation into the ability of fresh tissue slices to synthesize cholesterol. After incubation of rat liver in a physiological buffer to which had been added deuterio acetic acid we were able to isolate deuterio cholesterol. The synthesis takes place only under aerobic conditions which is not surprising since the synthesis of this complex alcohol certainly requires the addition of considerable energy which must arise from the oxidation of glucose.

Other experiments show that the cell system must be preserved for this reaction to take place. This also seems quite reasonable for it is quite likely that numerous enzyme systems cooperate to carry out the many reactions which must

occur between the two-carbon acid and the twenty-seven-carbon alcohol. It is probable that these enzyme systems must be suitably oriented spatially, for many of the intermediates as well as the end product must be quite insoluble in the tissue fluids.

This reaction proceeds at an appreciable rate *in vitro* in the presence of liver slices only. We may reasonably conclude that the synthesis of cholesterol in the intact animal occurs only in the liver.

If in the normal adult animal the amount of cholesterol is governed by the rates of synthesis and degradation, how can we explain the abnormally high cholesterol concentrations in the sera of some subjects? This may arise from two possible causes. If the synthetic rate becomes greater than normal then the amount of cholesterol will increase. Under the influence of the increased amount of cholesterol the amount of cholesterol degraded will increase until a new stationary state is attained. Similarly, if the rate of degradation becomes less than normal, a new stationary state will be attained in which the amount of cholesterol in the cell will be greater than normal. Since either explanation can account for high cholesterol values there may be two different types of hypercholesterolemia. The first type can be caused by an increased rate of production of cholesterol. This increase may occur as the result of the piling up of too high a concentration of the precursors of cholesterol. It may be that the hypercholesterolemia of diabetes belongs to this class. The other type can occur as a result of an inhibition of the rate of disposal of cholesterol.

There seems to be good evidence that cholesterol is converted to its excretory product coprosterol by being first oxidized to cholestenone and then reduced to coprosterol. An inhibition of any step in the series of processes leading to elimination could cause a hypercholesterolemia. A beginning in the solution of this problem thus depends on the determination of the rates of formation and decomposition of cholesterol in the normal and pathologic state. This is a conclusion we have come to in our consideration of many medical problems: it is important to obtain more kinetic data before these problems can be attacked in a rational manner.

The feeding of labelled acetate to intact animals leads to the formation not only of labelled cholesterol but also of labelled fatty acids, hemin, amino acids and uric acid. This suggests very strongly that acetic acid is a substance normally formed by the organism from one of the major dietary constituents. The fact that acetic acid is not found in the normal animal is not evidence against this view, for of necessity the substances which are formed in the chain of successive reactions which the organism employs for the oxidation of its diet must be highly reactive and must be destroyed as fast as they are formed. No one has isolated from the intact animal any of the many proposed intermediates of the metabolism of fatty acids or carbohydrates.

It is pertinent at this time to indicate why the roles which acetate plays in the synthesis of cholesterol remained unknown previously. There are at least two reasons for this. First, the rate of synthesis of cholesterol is quite small. Only about 2 per cent of the total cholesterol of the organism is excreted and

replaced by newly synthesized cholesterol per day. Even if the rate of cholesterol synthesis were increased by giving the organism an increased amount of acetate, the increase of total cholesterol over a period of a few days would not be significant. Secondly, the organism normally forms each day such a large amount of acetate that what would be considered large additions of acetate would not appreciably increase the total acetate available to the cell. Only by the use of the isotope technique could this reaction be found for in this case we rely not upon the increase of the absolute amount of cholesterol in the cell but on the appearance of the label in the newly formed molecule.

The chemical relationship between cholesterol and the bile acids suggested the possibility that there might be a metabolic relationship. To investigate this hypothetical connection cholesterol labelled with deuterium was fed to a dog. This animal had had its bile duct connected to the urinary bladder so that it excreted its bile acids in the urine. An emulsion of cholesterol was given intravenously. Since cholesterol is frequently given experimentally by this method

TABLE I

*Atom Per Cent Excess Deuterium in Tissue Cholesterol after Intravenous Injection of Deuterio Cholesterol (4.16 Atom Per Cent Excess Deuterium)*

ORGAN	D <sub>2</sub> EXCESS	ORGAN	D <sub>2</sub> EXCESS
Red blood cells.....	0.31	Pancreas.....	0.25
Plasma.....	0.33	Adrenals.....	0.30
Liver.....	0.71	Omentum.....	0.20
Kidney.....	0.31	Testis.....	0.15
Lungs.....	2.00	Brain.....	0.00
Heart.....	0.39	Spinal cord.....	0.00
Spleen.....	0.46		

it may be of some interest to see where the material finally deposits. The cholesterol was injected for three successive days and finally on the sixth day the animal was sacrificed. In Table I is shown the isotope concentration of the cholesterol of various organs. The highest isotope concentration was found in the lung sterols. As the lung is not particularly noted for its cholesterol metabolism, what we here observe is probably the filtering action of the capillaries of the lung. The next interesting value is that for the brain. None of the labelled cholesterol was deposited in the brain. Dietary cholesterol is not used by the brain. It is all manufactured *in situ*.

From the urine of this dog was isolated cholic acid. The cholic acid contained deuterium (Table II).

The cholesterol had been converted to cholic acid. Quantitative estimates suggest that at least half of all the cholic acid was derived from the cholesterol. This value, for reasons which time does not permit me to set forth, is a minimum value. It may well be that all the bile acids are derived from this substance.

I have spoken at such length of the cholesterol problem not only because of



its intrinsic significance but primarily because it so well illustrates the power and the scope of the isotope technique applied to a problem on which so much had been published and so little had been known.

The dynamic state is most clearly demonstrated by investigations of the cellular proteins. Here the rates of synthesis and of degradation are so rapid that it is clear that the structure and composition of the cell is to a large extent governed by kinetic factors.

In an adult animal in equilibrium the nitrogen excreted is exactly equal to the nitrogen intake. Of course, this is not true from moment to moment, but is so if experimental periods exceeding one day are taken. If the dietary nitrogen intake is suddenly increased the organism in response increases its excretion of nitrogen. That the excreted nitrogen is not the same as the dietary nitrogen was one of the first findings of the isotope technique. The results obtained after feeding glycine to human subjects in nitrogen equilibrium is shown in figure 2. Here adult subjects were given by mouth about 700 mg. of glycine labelled with  $N^{15}$ . By following the rate of excretion of  $N^{15}$  we can directly deter-

TABLE II

*Atom Per Cent Excess Deuterium in Cholic Acid and Bile Cholesterol after Intravenous Injection of Deuterio Cholesterol (4.16 Atom Per Cent Excess Deuterium)*

SAMPLE NO.	DAYS AFTER 1ST INJECTION	CHOLIC ACID	BILE CHOLESTEROL
I	1, 2	0.17	0.13
II	4	0.24	0.50
III	5, 6	0.16	0.29

mine how fast the nitrogen of dietary glycine is excreted. After 48 hours about 40 per cent of the labelled nitrogen has been excreted and then the excretory rate drops to a very low value. Only 40 per cent of the labelled glycine nitrogen has been converted to urea and ammonia, while 60 per cent is retained in the subject. We know that it cannot be retained as glycine for there is no reservoir of amino acids in the animal. The other 60 per cent must largely have been incorporated into protein. As the total amount of protein has not increased an equal amount of glycine present originally in the protein must have been liberated from the polypeptide and oxidized.

We cannot tell from this experiment how rapidly these reactions, the formation of proteins and their degradation, proceed but we can reasonably infer that they must be rapid. The synthetic reactions are sufficiently rapid to incorporate about 60 per cent of dietary amino acids into proteins. The actual determination of the rates of these reactions can be obtained only from experiments designed to study reaction rates. It is not possible to carry out such investigations on the human being. We, therefore, investigated the rates of protein formation in the rat. I shall later attempt to show you that the rate of protein formation, or chemically speaking, of peptide bond formation, is approximately the same in man as in the rat.

To investigate these rates a group of rats on a nitrogen low diet were given a supplement of glycine labelled with  $N^{15}$ . After three days they were continued on the basal diet. Thereafter, at short intervals groups of rats were sacrificed and the isotope concentrations in their proteins determined. Figure 3 shows how the isotope concentrations of the proteins of various organs varied with time. The dotted line labelled AIC is the average isotope concentration of the entire animals. As the animals are on a nitrogen free diet their average isotope concentration will not change appreciably. It seems natural to expect that the isotope concentrations of all tissues will, with time, tend to approach the average isotope concentration. Indeed, we see that this is the case. The liver which has the highest isotope concentration gradually falls to a lower value while the

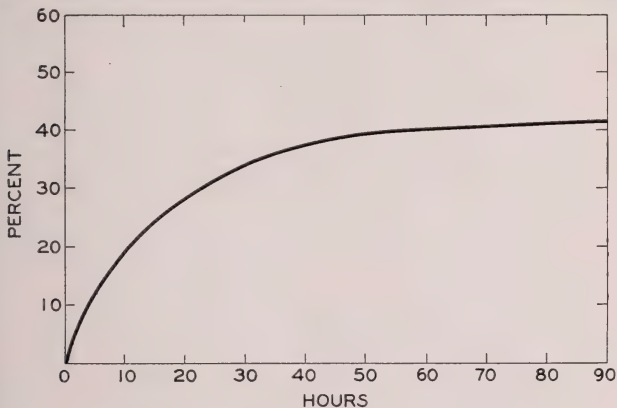


FIG. 2. Rate of Excretion of Labelled Glycine Nitrogen.

isotope concentration of the carcass gradually rises. I should like to point out that the fact that any isotopic nitrogen is present in the protein signifies that peptide bonds have been formed; protein has been manufactured. For the isotope concentration of the liver to fall it is necessary for amino acids having a lower isotope concentration to replace in the protein similar amino acids having a high isotope concentration. Since the animals in this experiment are on a nitrogen free diet, the only source of amino acids having a low isotope concentration is the carcass proteins, the muscles. The declining isotope concentration of the liver proteins is thus the result of the transfer of amino acids having a low isotope concentration. This replacement requires the rupture of the primary valence bonds of the protein and their reformation. From the rate of fall of the isotope concentration it is obviously possible to determine the rate at which liver protein, under the influence of the various enzyme systems, is

being degraded and resynthesized. From these data we calculated that half of the liver protein is being degraded and resynthesized in about six days. The liver indeed is involved in a set of rapid chemical reactions, not only those which it carries out for the rest of the organism but the apparently purposeless destruction and reformation of its own structure.

In this experiment we also studied some reactions in a tumor. Here the interpretation of the data is not so clear. The isotope concentration in the tumor, originally lower than that in the liver, first rises until it attains the same concentration as the liver then declines rather slowly. The problem is complicated by

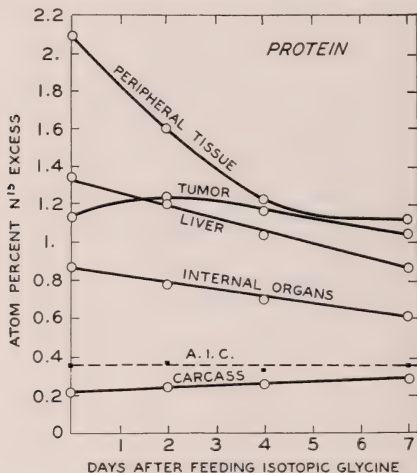


FIG. 3. Concentration of  $N^{15}$  in tissue proteins after feeding isotopic glycine. A.I.C. represents the average isotope concentration.

the fact that we are not dealing with a system in a stationary state, for the total mass of the tumor is increasing. At each moment more protein is being formed than is being destroyed. I shall shortly return to the problem of the growing tissue.

From the above values we can calculate that about 10 per cent of the liver protein of the rat is daily being regenerated. Not only the proteins are involved in this dynamic state but also its constituent amino acids. Isolation of individual amino acids from the liver protein reveals that not only is the labelled nitrogen present in the glycine, the labelled amino acid fed, but it is also present in other amino acids (fig. 4). Clearly the labelled nitrogen has been removed by some mechanism from the glycine and has been used for the synthesis of other amino acids. Simultaneously, nitrogen from other sources, hav-

ing a low isotope concentration has been employed for glycine synthesis. Again from the rate of decline of the isotope concentration of the liver glycine we can compute that half the glycine of the liver protein has been removed from peptide linkage and been replaced by other glycine molecules in a period of about six days. While we cannot directly deduce from this experiment the rates at which other amino acids are utilized for protein formation, other experiments have shown that at least leucine, lysine and histidine are about as reactive as glycine.

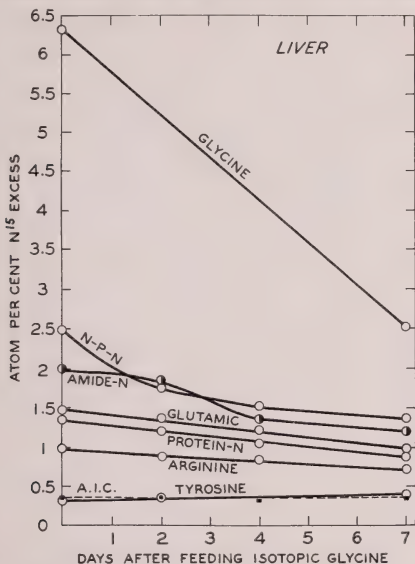


FIG. 4. Concentration of  $N^{15}$  in liver constituents after feeding isotopic glycine.

It seems quite probable at present that the same rates will be found for the rate of incorporation of other amino acids into proteins.

The synthesis of proteins occurs not only in systems in stationary states but also in cases where the total amount of the protein is declining. In collaboration with Dr. Heidelberger and Dr. Treffers, Dr. Schoenheimer and I some years ago undertook a study of the reaction of the specific proteins, the antibodies. Rabbits were immunized to type III pneumococci. Some time after the last injection of antigen, at a time when not only was the antigen not demonstrable but when the total amount of antibody protein was declining, labelled glycine was added to the diet. Despite the fact that the total quantity of antibody was declining, its isotope concentration rose during the feeding period (fig. 5). This can only

mean that during this period antibody was being formed. Since, however, the rate of synthesis of the antibody was lower than its rate of destruction the total quantity of antibody protein declined. After the cessation of feeding of labelled glycine the isotope concentration of the antibody declined for now the antibody was being synthesized with glycine which contained practically no heavy nitrogen. Again from the rate of fall of the isotope concentration, we concluded that about 6 per cent of the antibody was being synthesized per day, and about 10 per cent was being destroyed. An important question now arose. Is the

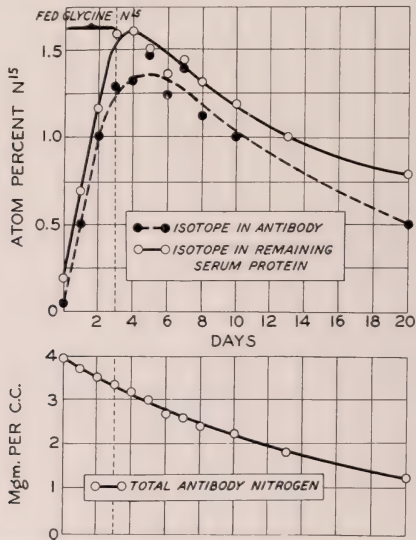


FIG. 5. Concentration of labelled nitrogen in serum protein and antibody of immunized rabbit during and after the feeding of isotopic glycine (calculated for an isotopic content of 100 atom per cent in the compound administered).

antigen necessary for the synthesis of the antibody, or can the antibody direct its own synthesis, i.e., is the antibody a self-duplicating organization? The ingenious techniques of the immunologist offered a method to solve the problem.

A rabbit was actively immunized to type III pneumococcus by injection of the antigen and passively immunized to type I pneumococcus by transfer of immune serum from another rabbit. Labelled glycine was then administered for three days and the specific antibodies isolated from the serum by precipitation with the specific polysaccharides. The results are quite illuminating (Table III).



The type III antibody, formed by injection of the antigen, contains  $N^{15}$ ; the type I antibody contains no  $N^{15}$ , it has not been synthesized. Synthesis of antibodies is not a self duplication phenomenon but requires the presence of the antigen. By extrapolating these data we may conclude that the other proteins similarly require the presence of some pattern for their formation. Proteins in general are not self-duplicating systems.

I have previously mentioned that we are quite ignorant of the factors which are involved in a growing system. Is growth the result of an acceleration of the synthetic processes which form proteins or is it the result of an inhibition

TABLE III

*Concentration of Marked Nitrogen in Type I and Type III Antibodies and in Supernatant Serum Proteins Obtained from Actively and Passively Immunized Rabbit after Administration of Isotopic Glycine*

The values are calculated for an isotope content of 100 atom per cent  $N^{15}$  in the administered compound. The probable error of these values is  $\pm 0.03$ .

PERIOD*	ANTIBODY TO C SUBSTANCE		TYPE I ANTIBODY		TYPE III ANTIBODY		SUPER- NATANT SERUM PROTEIN, $N^{15}$ CONCENTRATION
	Total N	$N^{15}$ concentration	Total N	$N^{15}$ concentration	Total N	$N^{15}$ concentration	
<i>hrs.</i>	<i>mg. per cc.</i>	<i>atom per cent</i>	<i>mg. per cc.</i>	<i>atom per cent</i>	<i>mg. per cc.</i>	<i>atom per cent</i>	<i>atom per cent</i>
0 (Before injection)	0.16				3.12	0.07	
0 (After " )	0.13		1.09	0.07	2.30†	0.10	
22½	0.12	0.40	0.68	0.03	2.59‡	0.42	0.55
			0.66§	0.09	2.70	0.43	0.54
48	0.12	0.73	0.49	0.12	2.27‡	0.86	1.06
			0.46§	0.05	2.30	0.85	1.07
168	0.07	0.62	0.18	0.10	1.52‡	0.68	

\* After the beginning of isotope administration.

† Probably too little S-III was used for the analyses.

‡ From the supernatant after removal of Type I antibody.

§ From the supernatant after removal of Type III antibody.

|| After 48 hours 56 cc. of blood were removed and a transfusion of normal blood given for survival. Five days later this sample was taken.

of the degradative mechanism? It is clear that either explanation could account for growth. A rat liver contains about one gram of protein. Our results indicate that daily one-tenth of a gram of protein is degraded and replaced by one-tenth of a gram of newly synthesized protein. If the synthetic rate were increased to 0.2 gm. per day and the degradative rate remained unaltered at 0.1 gm. per day, the total liver mass would increase by the difference, 0.1 of a gram per day. The liver would grow. On the other hand, if the degradative reactions were blocked the net increase of liver protein would also increase by 0.1 gm. per day. Growth can be explained by either mechanism. The isotope technique since it offers a method of measuring rates of protein synthesis can throw some light on this problem.

After some consideration as to the proper system to investigate, we chose to study the regeneration of the liver of the partially hepatectomized rat. It is possible here to remove up to 70 per cent of the liver without fatal consequences. The liver regenerates so rapidly that after 10 to 14 days it has regained its original mass.

Rats which had had about 50 per cent of their liver removed were, two days after operation, placed on a diet containing labelled glycine. To a first approximation the isotope concentration found in the liver protein is a direct measure of the rate of the synthesis of protein. In the normal animal the isotope concentration after one day on a standard diet rises to 0.063 per cent  $N^{15}$ . This is equivalent to a synthesis of 10 per cent per day. In our controls which had had the same surgical treatment as the partially hepatectomized rats, except that no liver tissue had been removed, the isotope concentration of the liver proteins after one day was 0.072 per cent, corresponding to a daily synthesis of 11 per cent. The hepatectomized rats' liver proteins had an isotope concentration of 0.082 per cent corresponding to a synthesis of 13 per cent of its liver protein per day. If the degradative reactions remained unchanged, the mass of the livers would increase by the difference between the synthetic and degradative reactions or 2 per cent per day. Actually the masses of these livers were increasing by 15 per cent per day. The only explanation of these data is that the degradative reactions have been appreciably inhibited. These livers are growing not because of an increase in the rate of protein synthesis but because of an inhibition of protein degradation. The earlier data on the tumor tissue in our rats is consistent with this hypothesis.

This interpretation of data from the growth experiment is in complete accord with our general beliefs about the dynamic state, for this theory suggests that reactions which can occur in a cell actually do take place at maximum speed. It is thus not easily possible to accelerate a reaction except by increasing the amount of available substrate or the amount of enzyme. While it is not easy to accelerate a reaction, it seems to be quite possible to inhibit one, as for instance by the inactivation of an enzyme system. There are many examples of such cases. In general, we are thus led to the conclusion that growth is the result of an inhibition. It would, of course, be most important to verify this generalization in some other growing systems and more especially in tumors. If this is found to be true in those systems, it would direct our attention into fields which are but little considered at present.

The processes we have here been observing are of a general nature. They involve primarily the formation and rupture of peptide bonds.

In an attempt to follow this process in the human subject, we fed to one of my colleagues, over a period of three days, 66 grams of  $N^{15}$  labelled glycine. At intervals blood samples were taken and the isotope concentrations of the serum proteins determined. As in the case of the rat the isotope concentration of these proteins rose during the feeding period and then declined. In the usual manner, we deduced that the average half life time of the human serum proteins is about 8 days; about the same period was found for the serum proteins of the rabbit

and the liver proteins of the rat. It should not be too surprising to us to find these values, obtained from such different animals, clustering about an average value of seven days. In all these instances we are probably observing the same chemical reaction, the formation and degradation of the universal peptide bond. It seems possible that the mechanism for the formation of the peptide bond is much the same in all living tissues. Further work will be necessary to confirm or disprove this hypothesis.

It is generally agreed that amino acids while primarily employed for protein formation, may have other functions in the organism. It is reasonable to suspect, at least, that histidine is the precursor of histamine and it is known that glycine is the precursor of glutathione and creatine. With the exception of these examples, we are quite in ignorance as to the function of any particular amino acid in the cell. I think it is almost obvious that each particular amino acid has a specific purpose other than that involved in the synthesis of protein.

For several technical reasons our laboratory has been particularly interested in the glycine problem. Last year, Dr. Shemin discovered that serine is a source of glycine in the organism. What uses does the cell make of glycine? This problem has no general solution. One must, after feeding labelled glycine, look for the marker in other compounds. In the human experiment I have just described, we had obtained as a by-product considerable amounts of red cells. The isotope concentration of these cells was quite low. Proceeding on the principle that as little as possible should be wasted in an isotope experiment, we isolated from these red cells some crystalline hemin, the protoporphyrin of hemoglobin. Isotope determination of this material gave striking results (fig. 6).

The isotope concentration rises for 20 days, levels off, and does not drop until the 90th day. This curve is qualitatively different from the curve we obtained from the proteins.

Such a curve cannot be the result of a single process involving molecules which are synthesized and degraded by a random process. If, however, a constituent of a cell is not involved in the flux of chemical reactions, the presence of  $N^{15}$  must be the result of the synthesis of the compound and its incorporation during the formation of the cell. These labelled molecules will then remain with the cell until it disintegrates. In the case at hand glycine is specifically used for the synthesis of the protoporphyrin. During the period in which labelled glycine was fed, heme containing isotopic nitrogen was formed and incorporated into the newly formed erythrocytes. As these are discharged into the circulation they increase the isotope concentration of the total red cells. These red cells circulate, unaltered, for over 80 days before some of them begin to be destroyed. The porphyrin liberated is not reutilized but converted to bile pigments and excreted. These cells containing  $N^{15}$  are replaced by cells containing no  $N^{15}$ , so that the isotope concentration drops. The average life span of the human erythrocyte can be evaluated from the time separating the mid-points of the rising and declining portions of the curve. This time is 127 days. This value for the life span of the human erythrocyte is the first one obtained under normal physiological conditions. It would of course be of greatest interest to establish the life

span of the red cell in some pathological states. Accumulation of such data may throw light on disturbances of the red cell which are of clinical importance.

From the urines of our subject we isolated samples of uric acid. This substance is believed to arise from the oxidation of the various purines. The isotope concentrations observed in the uric acid were much higher than might be expected from a substance arising from the breakdown of the nucleoproteins. It was clear that localization of the  $N^{15}$  in the ring system would be desirable. While we were studying this problem a group of investigators at the University of Pennsylvania sought for and found the sources of the various carbon atoms

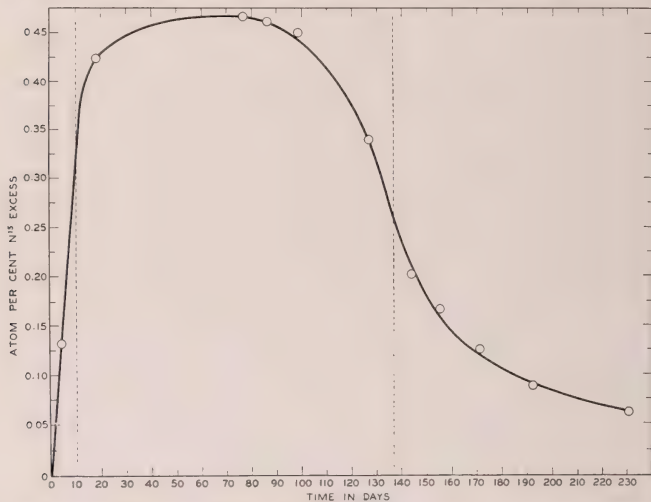


FIG. 6.  $N^{15}$  concentrations in hemin of human red cells after feeding labelled glycine for three days.

of uric acid in the pigeon. Sonne, Buchanan and Delluva found that carbon atom 6 arises from  $CO_2$ , while carbon atoms 2 and 8 arise from the carboxyl carbon of acetic acid. Carbon atom 5 is derived from the carboxyl group of glycine.

Though the metabolism of uric acid is quite different in the mammal from that of the bird, it is possible that the same synthetic mechanisms may operate in both. Breakdown and analysis of the various nitrogen atoms of uric acid show that the concentration of  $N^{15}$  in position 7 is so high that there can be no doubt that the amino group of glycine was the direct precursor. Taken with the results

of Sonne et al, it is clear that the entire molecule of glycine is employed in the synthesis of uric acid both in the pigeon and in man.

This brief survey of some of the applications of the isotope technique to problems of biology and medicine makes it clear that important contributions will be rendered by this technique in the future.

The work I have here presented was obviously the work of many hands and minds. The vital role which the late Dr. R. Schoenheimer played in the inception and development of this entire field must be familiar to all of you. More recently Drs. Shemin, Sprinson, Bloch and Sproul have been largely responsible for the data presented here. Without their collaboration and the critical evaluation of these results by my colleagues, Doctors Clarke, Miller and Foster, there would have been but little for me to report on tonight.



# INTESTINAL IRRIGATION IN THE TREATMENT OF CERTAIN TYPES OF UREMIA

## A PRELIMINARY REPORT

GORDON D. OPPENHEIMER, M.D. AND STEPHAN ROSENAK, M.D.

*(From the Urological Service, The Mount Sinai Hospital, New York)*

In many instances of azotemia, such as those caused by poisoning with heavy metals and other substances, transfusions of incompatible blood, obstruction by sulfonamide crystals, shock, and cystoscopic manipulation, recovery from the renal damage may occur and renal function may ultimately be fully restored if life can be prolonged by removal from the blood of the retained products of renal failure.

By means of dialysis, the peritoneum or other serous linings being used as a membrane, it was shown experimentally that urea, creatinine and other toxic and non-toxic crystalloids could be removed from the body. Putnam (1), Ganter (2), Rosenak (3, 4) and others were among the earlier investigators in this work. Rhoads (5), and Frank, Seligman and Fine (6) reported successful clinical applications of this method. Additional case reports have been published and undoubtedly unreported successful treatments have been given.

Kolff (7, 8) designed an ingenious apparatus for continuous dialysis of the blood outside of the body. The apparatus is effective; by means of it Kolff has been able to save a number of lives.

These methods involve certain drawbacks which must be overlooked because of the gravity of the disease. Thus with the "Kolff Kidney" the necessary heparinization of the patient may lead to hemorrhage. This apparatus cannot, therefore, be used on patients who have recently undergone surgical operation or in urological conditions where bleeding may occur. Furthermore, the procedure is dangerous in the presence of severe cardio-vascular disease. At present, children cannot be treated by the Kolff method because of the large volume of blood used in relation to the total blood volume.

Peritoneal lavage is hazardous in the presence of intestinal distention or peritonitis and the possibility of peritoneal infection is ever present. Some observers have reported difficulties with the outflow tube, which may become obstructed during peritoneal lavage. We believe this difficulty has been overcome with our new type of drain (9).

The knowledge that non-protein nitrogenous and other constituents of the blood can be removed from the blood into the lumen of the intestinal tract has not been utilized sufficiently as a method for reducing azotemia. Pendleton and West (10) in 1932 showed that when normal saline solution is introduced into an isolated loop of small intestine, its urea concentration quickly equalled or even slightly exceeded that of the blood. Wells' work (10) with dextrose showed that the exchange was reversible; Wells asserted that the mucosa acted as a

simple semi-permeable membrane. Kolff (11) spoke about the use of the intestine for lavage in uremia. Seligman, Frank and Fine (12) measured the urea clearance of the various parts of the intestinal tract. They found that the jejunum was the most effective region for this method. From one human experiment, using an isolated loop of terminal ileum, they concluded that the clearance of urea was too low to indicate that such a loop of bowel could act as a satisfactory substitute for the kidney. Rogers, Sellers and Gornall (13) of the University of Toronto proved that perfusion of the small intestine in dogs regularly resulted in lowered azotemic levels. They used a multi-channelled rubber tube. Physiological fluid was introduced above and was removed from the lowermost level. The irrigating fluid, used in quantities of 12 to 18 liters, contained 4.3 to 5.4 grams of non-protein nitrogen at the end of six hours.

Although we have worked with peritoneal dialysis, the simplicity of intestinal lavage has attracted us. A Miller-Abbott tube was modified so as to utilize its double channel. The tip was tied off and a rubber balloon partly filled with mercury was attached to it. Several openings were made in one channel near the tip. Four feet above the end, an opening was made in the other channel, for the introduction of the fluid. The fluid was to be aspirated from the lowermost openings by means of a Stedman pump attached to a closed carboy. This method was employed in the following case.

#### CASE REPORT

*History.* V. P., a negro, aged 39 years, was apparently in good health except for a urethral stricture, for which he received treatment periodically. He entered this hospital on October 4, 1947 with signs and symptoms of acute appendicitis. Appendectomy was performed; the pathological report was "chronic appendicitis with partial fibrous obliteration." The post operative convalescence was smooth, until about six days after the operation when he was found to have difficulty in urination. His blood urea nitrogen varied between 100 and 107 mg. per cent and the blood carbon dioxide combining power was found to be 26 volumes per cent. Hypochromic anemia was present. The blood pressure varied between 180 and 210 systolic and 120 diastolic. The urine contained moderate amounts of albumin (graded two to three plus), a few clumps of pus and a few red blood cells. It was possible to pass a small catheter into the bladder for continuous drainage, and to increase the size of the inlying catheter on alternate days until a #24 catheter was introduced. In spite of good drainage of urine with a low specific gravity, the blood urea persisted at levels around 90 mg. per cent. It was assumed that the renal failure was due to bilateral hydro-nephrosis and pyelonephritis secondary to prolonged urethral obstruction. Obviously an excretory urogram could not be performed. There was no evidence of urolithiasis. The patient was treated by careful regulation of fluid and chemical balance. One-sixth molar lactate solution and blood transfusions were given. Although the carbon dioxide combining power rose to 52 volumes per cent, the blood urea nitrogen remained unchanged. The patient refused permission for suprapubic cystotomy. Intestinal irrigation was then performed. The above described modified Miller-Abbott tube was passed through the nares into the mid-small bowel. The patient was ambulatory; he had not been vomiting and did not feel ill. However he was fasted for 24 hours before the treatment was given. By means of a 5 gallon carboy on a stand about 3 feet above the level of the bed, irrigating fluid was allowed to flow into the bowel. The fluid was recovered into a carboy placed on the floor and attached to the outflow channel; this carboy was subjected to negative pressure from a Stedman pump. The treatment was given twice. Four gallons were used the first

time on October 15th, over a period of 5 hours, and six gallons of fluid were given in 18 hours on October 16th and 17th. The composition of the irrigating fluid as expressed in grams per cent was as follows:

Sodium chloride.....	0.6690	
Potassium chloride.....	0.0040	
Calcium chloride.....	0.01327	(calcium 10.5 mg. %)
Magnesium lactate.....	0.0065	(magnesium 0.5 mg. %)
Acid sodium phosphate.....	0.0005	
Sodium bicarbonate.....	0.150	
Glucose.....	1.5	

in water.

Before irrigation the blood urea nitrogen fluctuated between 80 and 90 mg. per cent (Table I).

Immediately after irrigation the blood urea nitrogen was 46 mg. per cent.

TABLE I

DATE	BLOOD UREA NITROGEN	CO <sub>2</sub>	Ca	P
	mg. %	vol. %	mg. %	mg. %
October 10	107	16		
11	100	26		
13	80	52		
14	90		7.5	6.65
5 Hour Irrigation 15				
16 { A.M.	83	48.8		
P.M.	50			
18 Hours Irrigation 17	46			
18	55			
20	51			
21	58			
24	63			
27	71	33.2		
28	88			
Died November 3rd				

An analysis of the recovered irrigating fluid showed a total nitrogen content of 111 mg. per cent and 70 mg. per cent.

It should be noted that, at times, some difficulty was experienced in recovering the introduced fluid. The fluid which could not be recovered passed into the large bowel; this resulted in profuse watery diarrhea.

The patient left the hospital about 12 days after the intestinal irrigation but returned shortly thereafter with symptoms and signs of severe uremia with cardiac failure. He succumbed on November 3rd. Unfortunately no post-mortem examination was permitted.

The reduction in blood urea nitrogen from 90 to 46 mg. per cent is evidence of the efficacy of the method. In spite of continuous bladder drainage, the blood urea nitrogen rose progressively to 88 mg. per cent after the intestinal irrigation was discontinued.

#### COMMENT

This clinical trial indicates that irrigation of the jejunum may exert a beneficial effect in selected cases of azotemia provided a proper technique is employed. We believe that there are other significant factors besides dialysis to be considered

in this method. Full recovery of the irrigating fluid is of prime importance in order to prevent resorption of the nitrogen contained in it and to prevent over-hydration.

Since the return flow channel of the intestinal tube tends to become obstructed we are having a tube manufactured with a pliable circular spring which will keep the channel open. One limitation of this method is that in a distended uremic patient with vomiting, the passage of an intestinal tube may be impossible. In such instances, gastric lavage has been used, but our experience with it has not been favorable because too much fluid passed through the pylorus instead of returning via the tube.

It is therefore proposed, in suitable cases, to do a double enterostomy (Kader type) under local anesthesia. The upper stoma will be in the jejunum while the lower one will be placed in the ileum. Then, in similar fashion, irrigation may be accomplished without the drawbacks of intubation via the naso-pharynx.

It also seems feasible to us at this time to have a completely short-circuited loop of jejunum prepared for repeated irrigations in cases of chronic uremia.

The authors wish to thank Dr. I. Snapper for his encouragement and for the use of the facilities of his laboratory. They also are indebted to Dr. George Baehr and Dr. Saul Jarcho for constructive criticisms. Dr. Lester Narins and Dr. Joseph Sherman, Residents in Urology, cooperated in the clinical management of the case.

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## CONVULSIONS UNDER GENERAL ANESTHESIA

JULIUS BARCHAM, M.D. AND BERNARD H. ELIASBERG, M.D.

In 1927, active interest in convulsions occurring under general anesthesia was stimulated by the papers of Pinson (1) and Wilson (2) who described the phenomenon and gave their views as to possible etiological factors. Since that time, the literature has contained numerous reports on the subject, the majority of which were written by British authors.

A convulsion is an impressive occurrence under any circumstance, but when it manifests itself in a thoroughly relaxed patient under general anesthesia, it is all the more striking. Premonitory twitchings are frequently noticed first around the eyes and on the face. The twitchings soon spread to the upper extremities, the trunk, and the lower extremities. In an extremely short time the entire body is thrown into clonic convulsiform movements. The respiratory movements become irregular and may cease. Cyanosis may ensue, and progress rapidly to fatal asphyxia unless the proper therapeutic measures are taken. It is not difficult to differentiate clinically between a true anesthetic convulsion and the jactitations that may occur with a rapid induction (3).

The incidence of anesthetic convulsions varies in different institutions, but the average is probably that stated by Ray and Marshall (4), 1 in 6000 cases. An unusual feature of the five cases to be reported here is that they occurred in the short period of 137 days, during which time 894 general anesthetics were given on the ward service. This gives the unusually high incidence of 1 in 179 cases.

While many theories as to the etiology of these occurrences have been advanced, no single "cause and effect" relationship has ever been established. The very multiplicity of hypotheses advanced is ample proof that there is no one definite etiological factor. Lundy (5) lists 33 possible causes.

Pinson (1) believed that excess carbon dioxide was the responsible factor. Goodman and Gilman (6) state that the administration of 25 per cent carbon dioxide leads to muscle twitchings, clonic convulsions, and death from respiratory paralysis.

Ray and Marshall (4) emphasized the importance of anoxia, a factor of great significance. Hypoxia in some form is found in most of the cases reported in the literature. Deep anesthesia, by its toxic effect on the cell and by its depression of respiratory exchange and blood pressure, will produce histotoxic, anoxic, and stagnant anoxia. Hyperthermia, particularly in the younger age groups, with its accompanying elevated metabolic rate and oxygen demands, increases the tendency toward anoxia. These factors will also favor the retention of carbon dioxide. Severe sepsis will cause histotoxic anoxia. Another factor that may contribute to the development of anoxia is the relative or absolute over-dosage of pre-operative atropine; the mechanism of such action is either the elevation of temperature by suppression of sweating, or the specific stimulation of metabolism by atropine per se, or both. Minnitt and Gillies (7) suggest the possibility of anoxia localized to the cerebrum by obstruction of the venous



return from the brain as the result of pressure on the great vessels of the neck by the head-strap, and by the Trendelenberg position.

Ethyl ether has been considered an etiological factor. The incidence of convulsions under ether anesthesia was great enough to have the term "ether convulsions" applied to the phenomenon. However, convulsions have also been encountered with ethyl chloride (3), chloroform (8), nitrous oxide (9), cyclopropane (9, 10), vinyl ether (11), and ethylene (11). It is also significant that the great majority of general anesthetics entail the use of ethyl ether as the primary agent, which would proportionately increase the incidence of convulsions with this agent. Wilson (2) suggested impurities in ether as the factor responsible for the convulsions. However, Gold and Gold (12) have conclusively eliminated the possibility of the usual ether impurities (aldehydes and peroxides) playing a role in the production of anesthetic convulsions. Drum ether is used in this institution, but samples are frequently sent to the chemistry laboratory, where they are tested for impurities.

Idiosyncrasy to the anesthetic agent has been suggested as a basis for these convulsions but no evidence has been forthcoming to support this theory. Stein (13) described a case of proven idiosyncrasy to ethyl ether which was manifested by a state of shock.

Durrans (14) points out that while some anesthetists encounter this complication quite frequently, others never see convulsions in any of their patients. This is borne out by the experience of one of the authors (B. H. E.) who, in a series of approximately 50,000 anesthetics personally administered, has never encountered a convulsion under anesthesia.

Rosenow and Tovell (15) state that "ether convulsions are attributable to a neurotoxin or poison produced by some strains of streptococci in amounts insufficient to cause spasm in the absence of anesthesia, but which in the course of anesthesia suffice to incite the muscular spasms characteristic of this condition." Mousel (16) presented an interesting case which supports this theory. A child had three previous anesthetics with nitrous oxide and ether, in which no untoward incidents occurred, and no nasal cultures were taken. During the fourth anesthesia a convulsion occurred, and cultures taken immediately post-operatively showed the presence of neurotropic streptococci. The child was again anesthetized two weeks later. There were no convulsions and cultures taken then did not show streptococci. Rosenow and Lundy (17) presented additional cases favoring this theory.

Mortality figures have varied with the different authors. The figures range from 18 per cent (4) to 50 per cent (18). In the five cases presented in this paper, the mortality rate was 20 per cent.

#### CASE REPORTS

*Case 1.* C. B., a 38 year old white female, was admitted on September 5, 1946 with bilateral lower quadrant pain. On admission, her hemoglobin was 100 per cent, and her white count was 15,000, with 84 per cent polymorphs. On the fifth hospital day the patient vomited fecal material. A flat film of the abdomen showed small bowel obstruction. There was also evidence of a severe infection, as shown by a white count of 2,500 with a marked

shift to the left, which was confirmed by a bone marrow study. Pre-operative medication, consisting of 12 mg. morphine and 0.4 mg. atropine, was given at 8:00 p.m. on September 10, 1946. Immediately before induction her temperature was 103.6°F., blood pressure was 140 systolic and 80 diastolic, and her pulse rate was 136. Cyclopropane-ether anesthesia was started at 8:50 p.m. Two inches of small bowel was found to be incarcerated and partially strangulated in a small ventral hernia. The patient was carried in upper third plane of surgical anesthesia, with good respiratory exchange. No clinical signs of anoxia were evident. At 9:25 p.m. the anesthetist noted twitching of the face, which soon ceased. At that time, the blood pressure was 108 systolic and 60 diastolic, and the pulse rate was 152. A moment later the facial twitching recurred, soon spread to the arms, and in a short time the entire body was thrown into convulsive movements. The ether was stopped immediately, and the patient was flushed with oxygen. An endotracheal tube was passed to ensure a patent airway. One gram of calcium gluconate was given intravenously at 9:31 p.m. with no effect. At 9:40 p.m. 0.25 Gm. of sodium amytal was given intravenously and the convulsions stopped immediately. The operation was completed at 9:47 p.m. Post-operatively, the patient's temperature was 106°F., blood pressure was 60 systolic and 0 diastolic, and her pulse rate was 130. At 5:00 a.m. the next morning, her temperature was 103.8°F., blood pressure was 150 systolic and 90 diastolic, and her pulse rate was 144. A spinal tap done later was negative in all respects. A neurological examination revealed hyperactive reflexes throughout. The patient never regained consciousness, and died twenty hours after operation.

*Comment.* Despite the absence of clinical signs, anoxia was undoubtedly a factor of great etiological importance in this case. The deep anesthesia, sepsis, and hyperthermia definitely aided in the production of anoxia, and possibly increased the concentration of carbon dioxide in the blood. The post-operative clinical picture pointed to hypoxic damage of the central nervous system. Inasmuch as the severity of the pre-operative picture was out of proportion to the operative findings, one may postulate that some unrecognized morbid factors contributed to this anesthetic complication. One can only speculate on the outcome of this case if a barbiturate has been given earlier in the course of the convulsion.

*Case 2.* E. R., a 20 year old white male, complaining of pain in the right lower quadrant of 24 hours' duration, was admitted on the evening of October 13, 1946. Physical examination disclosed, aside from abdominal signs, a short systolic murmur at the apex. On admission, the patient's temperature was 100.6°F., his pulse rate was 82, and his respiratory rate was 18. His hemoglobin was 100 per cent, and his white blood count was 19,600. Pre-operative medication, consisting of 12 mg. of morphine, and 0.4 mg. atropine was given at 11:00 p.m. Nitrous oxide-oxygen-ether anesthesia was started at 12 midnight. An abscessed appendix was found, and an appendectomy was performed. Adequate muscular relaxation could be achieved only by third plane anesthesia, which was accompanied by short jerky respiratory movements. At 12:40 a.m., apparently without any premonitory twitchings, the patient suffered a generalized convulsion. The administration of ether was immediately stopped, and the patient was flushed with oxygen. At 12:43 a.m. 5 cc. of 2½ per cent sodium pentothal was given intravenously and the convulsion stopped immediately. At 12:55 a.m., when the operation was completed, the patient's temperature was 100.2°F., blood pressure was 124 systolic and 78 diastolic, his pulse rate was 84, and his respiratory rate was 20. The patient made an uneventful recovery and was discharged on the sixth post-operative day.

*Comment.* In this case sepsis, hyperthermia, deep anesthesia, and inadequate respiratory movements combined to create a fertile field for the production of hypoxia and hypercarbia.

*Case 3.* C. P., a 30 year old colored female was admitted on October 26, 1946 for repair of a urethro-vaginal fistula of five years' duration. In December, 1944, the patient had had a 50 minute operation under cyclopropane anesthesia and had exhibited no convulsions or jactitations. The past history and physical examination were non-contributory. The patient was pre-medicated with 0.1 Gm. secenal at 1:00 p.m. on October 27, 1946, and 100 mg. demerol and 0.4 mg. scopolamine at 2:10 p.m. Nitrous oxide-oxygen-ether anesthesia was started at 3:00 p.m. At induction, her blood pressure was 80 systolic and 40 diastolic, and her pulse rate was 80. At 3:35 p.m. her blood pressure had risen to 110 systolic and 76 diastolic, and her pulse rate was 110, where they remained constant. The patient was maintained at the border line of first and second planes of surgical anesthesia throughout the operation. At 4:25 p.m. twitchings were noted simultaneously in the face and arms, and the remainder of the body was thrown into convulsive movements almost immediately afterwards. The ether was turned off, the patient was flushed with oxygen, and endotracheal intubation was performed at 4:27 p.m. At 4:30 p.m. 5 cc. of 2½ per cent sodium pentothal was given intravenously, and the convulsion ceased before the needle was withdrawn from the vein. At 4:35 p.m. the blood pressure was 100 systolic and 40 diastolic, and the pulse rate was 110. The operation was completed at 4:40 p.m. and the patient was returned to the ward in good condition. The patient made an uneventful recovery and was discharged on the twelfth post-operative day.

*Comment.* None of the anoxia-producing factors emphasized in Cases 1 and 2 were present here. The patient was in good physical condition, well oxygenated, and in light anesthesia. The soda-lime was relatively fresh. The etiology of this convulsive seizure is obscure.

*Case 4.* M. G., a 24 year old white female was admitted on November 5, 1946 for repair of a saccular aneurysm of the right transverse cervical artery. The patient described a two week episode of emotional instability approximately four months before admission. Physical examination was negative except for the local pathology. On November 16, 1946, at 12:30 p.m. the patient received pre-operative medication consisting of 12 mg. morphine, and 0.4 mg. atropine. Pre-operatively, her blood pressure was 98 systolic and 50 diastolic, and her pulse rate was 84. Cyclopropane-ether anesthesia was started at 1:45 p.m. When surgical anesthesia was reached, blood pressure was 110 systolic and 70 diastolic, and her pulse rate was 120, where they remained. At approximately 3:20 p.m. tremors were noted in the face, and soon the entire body exhibited convulsive movements. The administration of ether was discontinued, and the patient was flushed with oxygen. At 3:25 p.m. 6 cc. of 2½ per cent sodium pentothal was given intravenously, with immediate cessation of the convulsion. There was no interference with respiration and the patient's color remained good throughout the convulsive episode. The blood pressure dropped to 88 systolic and 60 diastolic after the convulsion and remained there for the duration of the operation. The pulse rate and quality were unaffected by the convulsion. The operation was continued under cyclopropane for 15 minutes, and then ether was reintroduced cautiously, with no return of the convulsions. The operation ended an hour later and the patient was returned to the ward in good condition. The post-operative period was uneventful and the patient was discharged on the eleventh post-operative day.

*Comment.* Nervous instability has been mentioned as a possible etiological factor (5), but it is difficult to see how it could cause a generalized convulsion after 95 minutes of surgical anesthesia. The region in which the operation took place must also be considered inasmuch as changes in pressure at the carotid sinus may produce generalized convulsions (19). There was probably some traction on the sinus, which is said to be stimulated by cyclopropane, and depressed by ether (20). Thus, it is impossible to state which anesthetic agent predominated

here. Again, none of the anoxia-producing factors were present. It is significant that the readministration of ether did not result in a return of the convulsions.

*Case 5.* L. J., a 27 year old negress, complaining of chronic diarrhea, was admitted on December 26, 1946. Her past history revealed that she had been treated at another hospital in 1942 for rheumatic fever and ulcerative colitis, occurring simultaneously. The physical examination revealed nothing abnormal except early clubbing of the fingers. X-ray studies revealed evidence of colitis in the transverse and descending colon. On admission, the patient's hemoglobin was 47 per cent. On January 21, 1947, after repeated transfusion, her hemoglobin had reached 74 per cent. On January 24, 1947, the patient was brought to the operating room, where an ileostomy was performed. The pre-operative medication consisting of 12 mg. morphine and 0.4 mg. scopolamine was given at 12:40 p.m. Immediately before operation the patient's blood pressure was 80 systolic and 60 diastolic, and her pulse rate was 80. Ethylene-ether anesthesia was begun at 1:20 p.m. The operation was begun at 1:35 p.m. At 2:00 p.m. the blood pressure had risen to 120 systolic and 80 diastolic, and the pulse rate was 84. The patient was then in the third plane of surgical anesthesia, and exhibiting short and jerky respiratory movements. At 2:10 p.m. clonic convulsions were noted in the lower extremities. These soon spread upwards and involved the trunk, upper extremities, and the head and neck. The administration of ether was immediately stopped, and the patient was thoroughly ventilated with oxygen. Four minutes after the onset of the convulsion, 4 cc. of 2½ per cent sodium pentothal was given intravenously, with immediate cessation of the convulsions. At 2:25 p.m. the blood pressure was 100 systolic and 60 diastolic, while the pulse rate remained at 80. The operation ended at 2:35 p.m. and the patient was returned to the ward in good condition. The post-operative course was completely uneventful.

*Comment.* The factors most likely to have been responsible for the convulsions are hypoxia and hypercarbia resulting from the prolonged deep ether anesthesia. A unique feature of this case is the onset of convulsions in the lower extremities, in contrast to the more frequent onset in the head and neck.

Despite the fact that the etiology of convulsions under general anesthesia remains obscure, an attempt at the prevention of these convulsions is possible, if one bears in mind that they occur more frequently in young patients exhibiting signs of sepsis and toxemia. In these cases, some form of anesthesia other than inhalation should be administered, if feasible. Intravenous sodium pentothal, spinal, local, or refrigeration anesthesia do not produce convulsions in this type of case. If, however, despite these considerations, inhalation anesthesia remains the method of choice, agents other than ether should be considered, as by far the greatest incidence of anesthetic convulsions have occurred with this agent. It would probably be wise to omit, or reduce the dose of atropine in the pre-operative medication of these selected cases. The addition of a barbiturate to the pre-operative medication would be advantageous.

If a convulsion does occur under general anesthesia, the most effective treatment is the intravenous administration of a barbiturate. Sodium pentothal, whose action as a cerebral depressant is both rapid and effective, is most frequently used for this purpose. Recently, Greenfield (21) presented a case of anesthetic convulsions that was successfully treated with intravenous curare.

However, more work must be done on the use of curare in convulsions before it can be recommended.

In addition to drug therapy, every effort must be made to support respiratory exchange, and cardio-vascular function. A patent airway must be established, and artificial respiration with oxygen is to be instituted if necessary. Intravenous fluids, and analeptics should be administered as the necessity arises.

#### SUMMARY

1. Five cases of convulsions under general anesthesia have been presented.
2. Although the incidence is usually low, anesthetic convulsions may occur, over short periods, with alarming frequency.
3. Careful evaluation of patients, and selection of techniques, premedication, and anesthetic agents may help reduce the incidence of this anesthetic complication.
4. Intravenous sodium pentothal is the drug of choice in the treatment of convulsions under general anesthesia.

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# ANEURYSMS OF THE ANTERIOR PORTION OF THE CIRCLE OF WILLIS CAUSING CEREBRAL HEMORRHAGE\*

MORTIMER OSTOW, M.D. AND SIDNEY BERMAN, M.D.

(New York, N. Y.)

Rouchoux (1), a little more than 100 years ago expressed the view that spontaneous intracerebral hemorrhage was always preceded by softening of surrounding brain tissue. He based this thesis upon the observation that no matter how soon death supervened following apoplexy, a narrow zone of softened tissue surrounded the region inundated by hemorrhage. Although eagerly accepted by many of Rouchoux's contemporaries, this view had subsequently fallen into discard, until in 1927, Globus and Strauss (2) again demonstrated disintegrating and reactive changes in the vicinity of spontaneous intracerebral hemorrhage and offered evidence that these changes anteceded the hemorrhage.

Physical and chemical factors were considered responsible for this effect. First, to contain the vascular stream, the wall of an artery must be able to withstand a pressure no less than the difference between the lateral blood pressure and the pressure of the surrounding medium. A diminution in the latter will increase the pressure differential perhaps beyond the tolerance of a diseased vessel. Second, when rupture has already occurred, the rate, and ultimately the amount of bleeding is determined not only by the size of the defect in the vessel wall and the height of the intravascular pressure, but also by the pressure level of the surrounding material as determined by its tensile strength. Thus, bleeding into softened tissue is likely to be more rapid and more extensive than bleeding into normal tissue. Finally, necrotic tissue contains enzymes and products of disintegration which can erode and weaken an exposed vessel wall.

In 1943, Globus and Globus (3) invoked this thesis to illuminate the problem of hemorrhage into the brain substance consequent to rupture of a cerebral aneurysm. In the cases presented, aneurysms, either encroaching upon, or enclosed within, brain tissue, had ruptured and bled into the tissue and thence into the ventricle. In each case pre-existing softening was evident. The softening was thought to be secondary to the direct mechanical throb of the aneurysm or to inadequate blood flow through its branches. It was inferred that the softening might have contributed to the rupture of the aneurysm. Microscopic study disclosed disorganization of the tissue adjacent to the area of hemorrhagic extravasation. There were ring hemorrhages, small aggregations of compound granular cells and an occasional ameboid glia cell. More peripherally, numerous hyperplastic fibrous astrocytes were encountered. In three of the ten cases described, the aneurysm involved the anterior communicating artery; in three others it involved the anterior cerebral artery; one aneurysm involved the internal carotid at its junction with the anterior cerebral; two involved the middle

\* From the Neuropathological Laboratory, The Mount Sinai Hospital, New York.

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cerebral artery and one, the posterior communicating artery. In no instance in the authors' material had aneurysms of the posterior cerebral or basilar arteries bled into a surrounding zone of encephalomalacia.

Two cases of rupture of aneurysm of the anterior half of the circle of Willis are presented to emphasize the constancy of the anatomical pattern.

#### CASE REPORTS

*Case 1. History.* (P.M. #12538) A man, aged 47 years, was admitted to the Mount Sinai Hospital on June 18, 1943 in coma. He was said to have been well until the previous afternoon when he had first complained of headache, and coma soon supervened.

*Examination.* On admission the patient was comatose and cyanotic. Temperature was 100°F. Breathing was noisy and periodic. Breath sounds were prolonged in expiration. Sonorous, sibilant and moist expiratory rales were heard over both lung fields. The pupils were miotic and did not respond to light. There was ptosis of the left upper eye lid. The extremities were spastic and the deep reflexes were overactive; bilateral ankle clonus and a Hoffman sign on the right were elicited. The Babinski sign was obtained bilaterally. No signs of meningeal irritation were noted.

*Course.* Lumbar puncture was performed and yielded grossly bloody cerebrospinal fluid under an initial pressure of 600 mm. of water. Upon removal of 15 cc. of fluid the pressure dropped to 300 mm. of water. The patient's cyanosis increased, his breathing became increasingly irregular, and shortly thereafter ceased, as did the heartbeat. Four cc. of epinephrine and 4 cc. of coramine were promptly injected intracardially and cardiac pulsations reappeared. At this time the pupils were dilated and numerous retinal hemorrhages were seen. Despite artificial respiration and administration of oxygen, respiration was not resumed and the patient died three hours after admission.

*Necropsy findings. Gross.* The general post mortem examination revealed moderate hypertrophy of the left ventricle, and slight hypertrophy of the right. Moderate coronary sclerosis without narrowing was noted.

A moderate amount of blood was spread diffusely throughout the subarachnoid spaces, most marked over the base of the brain and in the cisterna magna. The brain was somewhat softer than normal and appeared diffusely swollen. When the brain was removed, a tear in the left temporal lobe exposed the left temporal horn which contained blood clot. The arteries at the base of the brain appeared normal.

On sectioning of the brain, the entire ventricular system was found to be markedly distended and filled with partly coagulated blood. The ventricles in all compartments, including the fourth ventricle and the aqueduct of Sylvius, were symmetrically enlarged. In the region of the anterior extremity of the internal capsule, at its ventral portion and the adjacent portion of the putamen, there was a large area of discoloration (fig. 1). It bordered upon the anterior horn of the lateral ventricle and was in all probability the area of softening into which the hemorrhage had taken place and from which extravasation into the ventricles had followed. A small calcified aneurysm arising from the base of the anterior cerebral artery was found in the region of the hemorrhagic softening.

*Microscopic observations.* A section of the brain in the area of hemorrhage, stained with hematoxylin and eosin, showed in addition to a large accumulation of blood in the subarachnoid space, an area of massive extravasation into brain tissue, sharply demarcated from the adjacent, relatively intact tissue. Within the hemorrhagic area there were numerous fragments of capillaries and larger blood vessels. In other parts of the cerebral cortex there was rarefaction.

A section through the aneurysm of the anterior cerebral artery close to the point of rupture showed irregular dilatation, hyaline degeneration, and thread-like thinning of the wall (fig. 2). Other large arteries at the base of the brain showed thick atheromatous plaques, intimal proliferation and hyalinization (fig. 3).

*Comment.* Through a defect in an aneurysm, situated at a point of origin of the anterior cerebral artery, hemorrhage occurred and the blood invaded the adjacent brain tissue through which it burrowed into the neighboring ventricle. Vessels of the circle of Willis were the seat of intimal proliferation, hyalinization,

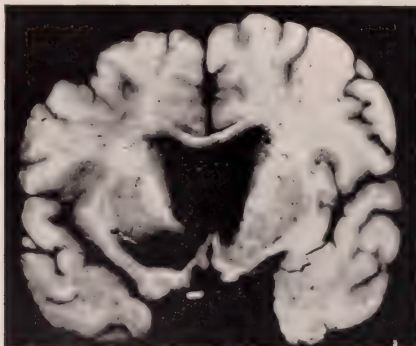


FIG. 1. Location of intracerebral hemorrhage and its point of rupture into the lateral ventricle.

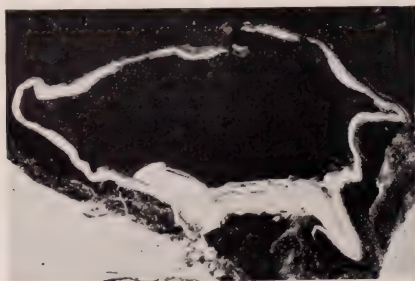


FIG. 2. Section of an artery in the neighborhood of the aneurysm showing thinning irregularity and hyalinization of its wall.

separation of media, and atheromatosis. No focal signs of softening preceded the apoplectic event since the area affected was a clinically silent one.

*Case 2. History.* (P.M. #13272) A housewife, aged 47, was admitted to the Mount Sinai Hospital on November 26, 1945 in coma. She was known to have had mild hypertension for several years. Two weeks before entering the hospital she had suffered an episode of headache and faintness. On the morning before admission she again developed a severe occipital headache. Shortly thereafter, her blood pressure was found to be 190

systolic, 100 diastolic. Hypodermic medication was administered at noon. In the course of a few hours the patient became increasingly unresponsive and by evening she was comatose and her blood pressure had risen to 250 systolic, 140 diastolic. The neck was not rigid but a bilateral Babinski sign and bilateral ankle clonus were observed. She passed through a convulsive seizure at midnight and again one hour later. The second episode ceased following the intravenous administration of 180 mg. of sodium amytal. Her mother and brother had diabetes mellitus.

*Examination.* The patient was comatose; skin was warm and dry and face was flushed. A sweetish odor was detected in the breath. Respirations were 30 per minute and Kussmaul in type. Lungs were clear to percussion and auscultation. The heart was not enlarged. A systolic murmur was heard over the base. Blood pressure was 165 systolic, 85 diastolic and pulse, 78. Temperature was 100.5°F. Pupils were small and equal. The right eye deviated laterally. Kernig and Brudzinski signs were not elicited. The deep reflexes were depressed in the upper extremities and overactive in the lower extremities. The Babinski sign was no longer present.



FIG. 3. Section of an artery at the base of the brain showing a large atheromatous plaque

*Laboratory data.* Initial urine specimen yielded 4 plus test for sugar and 2 3 plus test for acetone. An hour later albumin appeared in the urine. Hemoglobin was 80 per cent; white blood cells, 15,500; polys, 86 per cent; lymphocytes, 14 per cent;  $\text{CO}_2$ , 50 vol. per cent; blood sugar, 55 mg. per cent.

*Course.* Insulin and intravenous infusion of glucose and saline were administered. Acetone was no longer detected in the urine and the patient seemed more responsive until 5:30 a.m. when breathing became stertorous and the pulse rate dropped from 90 to 68 per minute. At that time the right pupil was dilated, the disc margin on that side was blurred and fresh retinal hemorrhages were observed. A spinal tap showed grossly bloody fluid under a pressure of more than 250 mm. of water. The patient died twenty-two hours after admission.

*Necropsy findings. Gross.* The general post mortem examination revealed cardiac hypertrophy and arteriosclerosis of the aorta.

The brain showed evidence of having been under increased intracranial tension; the gyri were markedly flattened, particularly over the mid-frontal region of the right hemisphere. There was marked discoloration on the under surface of the brain due to accumulation of blood in the subarachnoid space. There was a light, brick red discoloration on the dorsal longitudinal border of both hemispheres. The vessels at the base of the brain were

moderately thickened, particularly in the region of the pons. No aneurysm was discerned on the surface of the brain.

On sectioning of the brain, an area of hemorrhagic softening was found in the left hemisphere directly above the gyrus rectus. This area of softening communicated with the

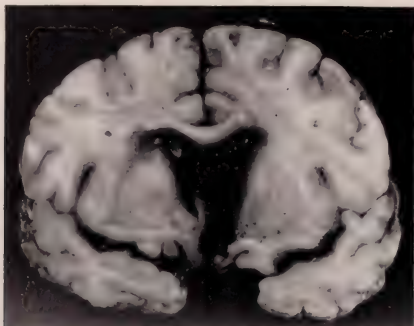


FIG. 4. Location of intracerebral hemorrhage and its point of rupture into the lateral ventricle.

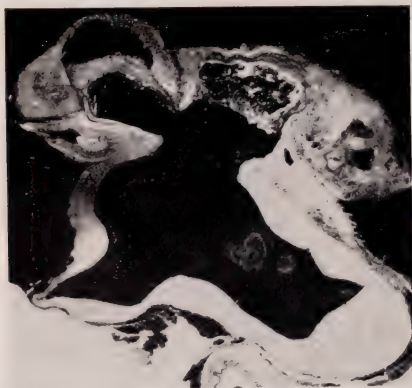


FIG. 5. Section of an artery in the neighborhood of an aneurysm showing an intraluminal hemorrhage and thinning, hyalinization and irregularity of its wall.

anterior horn of the ipsilateral lateral ventricle (fig. 4). The latter was filled with blood and was larger than the ventricle on the right. The entire ventricular system including the aqueduct and fourth ventricle was filled with blood.

*Microscopic observations.* A section of brain tissue in the region of the optic recess of the third ventricle, stained with hematoxylin and eosin, showed small areas of rarefaction and,



occasionally, very small areas of hemorrhage. There was marked capillary dilatation. The vessels showed moderate thickening and degenerative changes. Occasional focal areas of gliosis were noted.

In serial sections, the larger vessels revealed marked degenerative changes. One large artery showed hyaline degeneration of its wall and in various places extreme thinning and redundancy as seen in aneurysmal dilatation (fig. 5). One section of this aneurysm revealed an intramural hemorrhage. Intimal proliferation, separation of the media, and loss and distortion of the elastica interna were noted in the involved vessels.

*Comment.* In a patient, previously asymptomatic, profoundly degenerated walls of the major cerebral arteries and rarefied brain tissue suddenly yielded and massive hemorrhage into the left hemisphere above the gyrus rectus, ensued. In this case too, the rarefaction failed to show clinical signs because the region affected is usually clinically silent.

#### SUMMARY

Rupture of an aneurysm of the anterior portion of the circle of Willis has been demonstrated in two cases. In each instance, blood inundated the adjacent portion of the brain and penetrated into the lateral ventricle. The relatively more frequent occurrence of intracerebral hemorrhage in instances of rupture of aneurysms of anterior cerebral or anterior communicating is emphasized. Globus' suggestion that antecedent softening might facilitate intracerebral hemorrhage or rupture of cerebral aneurysm is reviewed.

The authors wish to acknowledge a debt of gratitude to Dr. J. H. Globus for his kind and wise supervision in the preparation of this paper.

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# AURICULAR TACHYCARDIA AND AURICULO-VENTRICULAR DISSOCIATION FOLLOWING 1.2 MG. OF DIGITOXIN IN ONE DOSE

JACOB STONE, M.D.\*

[New York, N. Y.]

It has been advocated chiefly by Gold and his co-workers, that digitoxin be used in the amount of 1.2 mg. in a single oral dose in order to digitalize patients who have not had the drug recently. Gold (1) has stated that "digitoxin has the advantage over digitalis leaf in that it is possible to induce the full effect with a single dose given at one time, in a period of six to ten hours in the place of the fractional dose method by which digitalis is used and which requires from twenty-four to forty-eight hours for the full effects. Local gastrointestinal irritation is negligible with this drug because the total dose of 1.2 mg. is too small to produce that effect." In a review of cardiac therapy, Gold (2) has stated furthermore that "from our experience with more than 1,000 single dose digitalizations with 1.2 mg. a negligible number, about 2 out of 100, show nausea and vomiting. The safety of this method is therefore beyond question."

The following case report is presented because it indicates that a single oral dose of 1.2 mg. of digitoxin may be excessive in some persons and produce toxic manifestations.

## CASE REPORT

*History.* (Adm. # 561023) M. F., man of 59 years was admitted to The Mount Sinai Hospital, New York, February 25, 1947. Nine years ago the patient experienced severe crushing chest pain which was diagnosed as coronary occlusion. Three years ago the patient was given digitalis and mercurhydrin because of shortness of breath and he continued taking the digitalis until six weeks prior to admission. He then felt well and discontinued all medication. Two weeks prior to admission he developed ankle edema, moderate shortness of breath, orthopnea, and epigastric pain. A control electrocardiogram (fig. 1 B) taken just prior to admission (February 25, 1947) was similar to that of April 20, 1946 and showed regular sinus rhythm, prolongation of the P-R interval to 0.24 seconds, slurring of the QRS, T waves diphasic or low in all three standard limb leads. These changes were considered indicative of myocardial damage.

*Examination.* Physical examination revealed a thin, small man, with markedly distended neck veins, dyspnea and orthopnea. His weight was 125 pounds. Moist rales were heard at both lung bases. The heart was enlarged to the left and a grade 2 apical systolic murmur with gallop rhythm was present. The second pulmonic sound was accentuated. The apical and radial pulse were equal, regular and 90 per minute. The blood pressure was 112 systolic and 78 diastolic. The liver was palpably enlarged three finger breadths below the costal margin and there was marked pitting edema of both legs. There was a positive hepato-jugular reflux, since right upper quadrant compression caused a rise in the apparent venous pressure with increased distention of the neck veins. The venous pressure was 20 cm., rising to 25 cm. on right upper quadrant pressure. The arm-to-tongue circulation time was 45 seconds (calcium gluconate).

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\* Fellow of the Dazian Foundation for Medical Research. From the Cardiographic Department, The Mount Sinai Hospital, New York, N. Y.

*Course.* On the evening of admission (February 25, 1947) the patient was given 1.2 mg. of digitaline nativelle orally in one dose and 2 cc. of mercurhydrin was administered intravenously. An electrocardiogram (fig. 2 A) taken the following day showed complete heart block with auricular tachycardia (rate 150-155) and ventricular rate 70-80. The ventricular rhythm was interrupted by numerous ventricular premature contractions forming periods of bigeminal rhythm. The QRS of the normal beats was slurred and widened to 0.12 seconds. Small Q-2 and Q-3 were present. RS-T-1 and RS-T-2 were depressed.

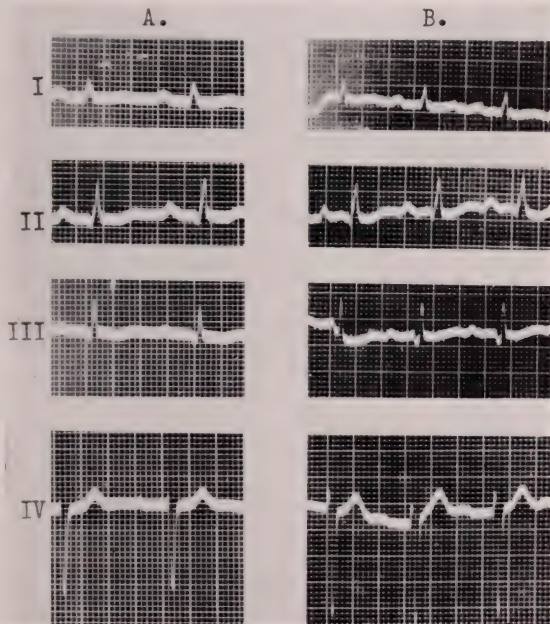


FIG. 1. M. F., man of 59 (Adm. # 561023). E.C.G. (A) 4/20/46, a regular sinus rhythm, rate 75 per minute with a prolonged P-R of 0.24 sec. QRS slurred, T-waves low or biphasic in three standard limb leads. Control E.C.G. (B) taken 2/25/47, just prior to admission, is essentially the same, regular sinus rhythm, rate 95 per minute.

The arrhythmia was considered to be a toxic manifestation of digitoxin. Despite this electrocardiographic evidence the patient did not exhibit any subjective signs of toxicity. Digitoxin was discontinued and serial electrocardiograms were taken, as follows: February 27, 1947: Auriculo-ventricular dissociation and frequent ventricular premature beats were still present with periods of 2:1 heart block (fig. 2 B). February 28, 1947: Regular sinus rhythm and an occasional ventricular premature beat were now present with first degree heart block. The P-R interval was prolonged to 0.28 second (fig. 3).

The patient still had signs of congestive heart failure with the liver enlarged four finger

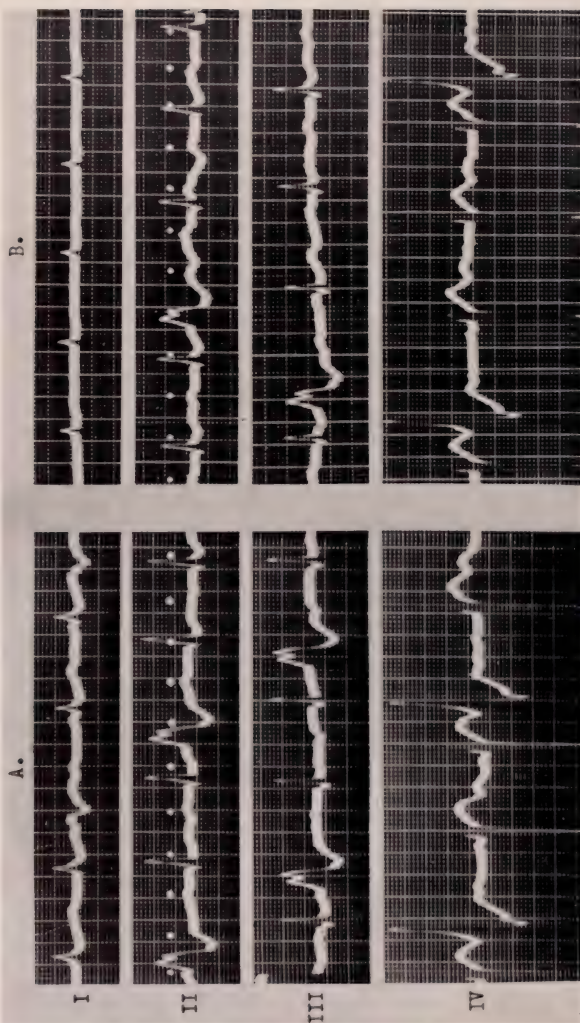


FIG. 2. Digitalis intoxication. Coronary artery disease with heart failure. Given 1.2 mg. digitoxin orally on admission, 2/25/47. No digitalis for 6 weeks. E.C.G. (A) next day, 2/26/47, complete heart block with an auricular tachycardia rate of about 150-155 per minute and a ventricular rate of about 70-80 per minute. White dots represent P or auricular waves. Many ventricular premature beats. Digitalis discontinued. Next morning, 2/27/47, E.C.G. (B) A-V dissociation still present. Clinically, no evidence of digitalis intoxication.



breadths below the costal margin and a few rales at the right lung base. There was moderate pretibial edema. The patient continued to receive mercurial diuretics and later was placed on a small maintenance dose of digitalis. On a low-salt, restricted fluid regimen with bi-weekly injections of mercurhydrin his failure gradually subsided. X-ray examination of the gastro-intestinal tract revealed the presence of an ulcer crater on the lesser curvature of the stomach. He was placed on an ulcer routine with complete disappearance of his gastrointestinal symptoms. He was discharged from the hospital improved on March 20, 1947.

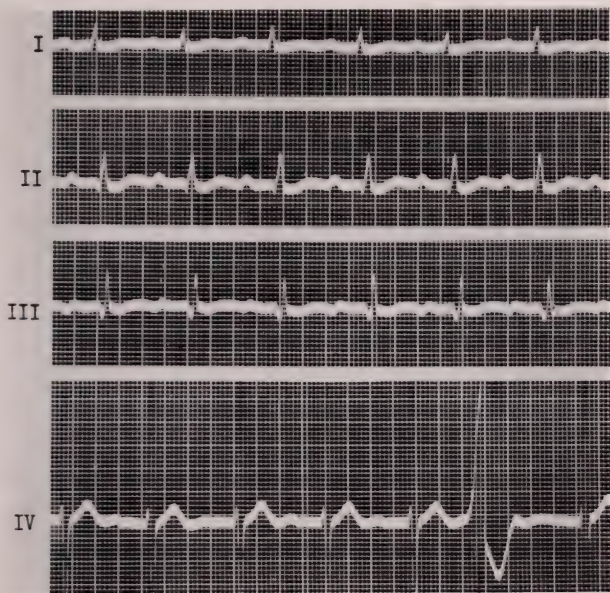


FIG. 3. Digitoxin intoxication. Coronary artery disease with heart failure. E.C.G., 2/28/47, a regular sinus rhythm, rate about 80 per minute with a prolonged P-R of 0.28 second.

#### DISCUSSION

This case offers conclusive evidence that occasionally 1.2 mg. of digitoxin given in one dose may produce toxic effects on the heart and thus may be hazardous. Digitalization should be an individual procedure and should take into account the weight of the patient. In the present case the weight was 125 pounds and it might have been suspected that the patient would require less than the usual dose of 1.2 mg. advocated by Gold. Furthermore, unless very rapid digitalization



is required, it may be worthwhile to administer the digitoxin in two or three divided doses.

The mechanism of the arrhythmia produced by digitoxin in this patient is of interest. The auriculo-ventricular dissociation probably was caused by depression of conduction through the A-V node and bundle of His as a result of stimulation of the vagus nerve and also probably by the direct action of the digitoxin on the bundle. Auricular tachycardia alone, in the presence of a depressed or poisoned A-V node or bundle, may result in complete heart block simply because the affected A-V node or bundle cannot transmit the shower of impulses. When part of the 1.2 mg. of digitoxin was eliminated the auricular tachycardia and the A-V dissociation disappeared but there still was evidence of toxicity in the prolongation of the P-R interval to 0.28 sec. (fig. 3).

#### SUMMARY

1. A case of toxicity due to 1.2 mg. of digitoxin given in a single dose is reported and the electrocardiograms taken the following day showing auricular tachycardia with complete A-V dissociation are illustrated.

2. In this patient, a man weighing 125 pounds, 1.2 mg. of digitoxin was excessive as the initial oral digitalizing dose.

I wish to express my appreciation for the assistance given by Dr. Arthur M. Master in the preparation of this paper.

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## FOREIGN BODY IN SECOND PORTION OF DUODENUM PERFORATING PELVIS OF RIGHT KIDNEY\*

M. JUDSON MACKBY, M.D.

The case to be reported is almost identical with one reported by McEnery and Fox (1). They described a two year old boy subject to persistent pyuria and intermittent fever. X-ray studies revealed a bobby pin in the second portion of the duodenum extending into the kidney pelvis. The pin was removed. In neither their case nor in ours was there a history of ingestion of a foreign body.

### CASE REPORT

*History.* The patient, a girl aged three years, was brought to The Mount Sinai Hospital on September 18, 1946. For the previous six months the child began to wet the bed frequently and had marked urinary frequency. Her urine became cloudy. There was no dysuria. Four months before admission to the hospital she had a fever ranging between 102° to 104° F. This lasted for a period of two months. She was given penicillin without appreciable effect. She was seen for the last three months in the Out Patient Department without discovery of the cause and without effecting a cure of the persistent pyuria.

*Examination.* The patient was a well developed, somewhat pale and undernourished child. There was slight deep tenderness in the right upper quadrant with an indefinite sensation of a mass in this region. There were no other physical abnormalities.

*Laboratory data.* The urine showed 2 plus albumin and was loaded with white blood cells. The blood count was hemoglobin, 79 per cent; white blood cells, 5150; segmented, 49 per cent; non-segmented, 16 per cent; lymphocytes, 35 per cent. Intravenous pyelogram taken on September 21, 1946 showed normal kidney function and excretion of dye. The calyces appeared normal. In the region of the right kidney a bobby pin was visualized. Further x-ray studies indicated that the bobby pin was probably in the second portion of the duodenum, with one end perforating the duodenal wall into the kidney pelvis. Cystoscopy was performed on October 3, 1946 and pus was found on catheterization of the right ureter.

*Operation.* (October 11, 1946) The peritoneal cavity was entered through an upper right rectus muscle splitting incision. The gall-bladder, hepatic flexure of the colon, and stomach were adherent and had to be separated to disclose the duodenum. A foreign body could be palpated in the second portion of the duodenum with the major portion extending into the right renal pelvis. A purse string suture was placed in the anterior duodenal wall and a small incision was made within this area. A hemostat was inserted through the incision and the bobby pin grasped between its jaws and extracted. The purse string suture was tied and a layer of interrupted Lembert sutures superimposed. The abdomen was closed in layers without drainage.

Convalescence was uneventful and the child was discharged on the 14th post-operative day. At the time of discharge there were 3-5 white blood cells in the urine and a very faint trace of albumin.

*Comment.* The bobby pin which must have been in its terminal location for six months had probably been lodged in this region because it was too long to make the turn from the second to the third portion of the duodenum, and eventually eroded the duodenal wall. This case, as well as the other reported by McEnery and Fox, illustrates the importance of a complete genitourinary investigation in a child with persistent albuminuria.

\* From the Surgical Service of Dr. John H. Garlock.

## SUMMARY

A bobby pin lodged in the second portion of the duodenum and perforated the posterior duodenal wall, entering the kidney pelvis with the production of persistent albuminuria. The bobby pin was removed transduodenally without difficulty and was followed by symptomatic relief. This case is identical with one reported in August, 1946.

## REFERENCE

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## EFFUSION IN THE TEMPOROMANDIBULAR JOINT COMPLICATED BY OTITIS MEDIA

JOSEPH G. DRUSS, M.D.

Diseases of the temporomandibular joint, because of its close proximity to the middle and external ear, are of particular interest to the otolaryngologist. Pain in and about the ear, facial neuralgia, tinnitus and stuffiness in the ear, among other symptoms, have been attributed to disturbances in function of this joint (1). However, contrary to expectation, extension of a contiguous inflammatory process from within the middle ear to the temporomandibular joint is rarely encountered, and only severe otitic infections such as those due to scarlet fever or measles have been reported to extend to the joint (2). Moreover, extension of infection from within the temporomandibular joint to the middle ear takes place even less frequently. Rupture of a neglected suppurating joint through the tympanic plate with drainage into the external canal has been observed.

Of the many causes ascribed to temporomandibular joint inflammation trauma is the most common one, with acute and chronic rheumatic fever, gonorrhea and other acute infectious diseases holding a minor place among etiologic agents. The degree of inflammation in the joint is usually not dependent upon the severity of the trauma and the clinical symptoms may become evident immediately following the injury or weeks later. In the case herein reported the clinical signs did not appear until one week after a relatively slight injury to the head.

### CASE REPORT

*History.* J. W., a nine year old girl, eleven days prior to her admission to the hospital, fell from a tricycle striking her head on an iron bed-post. There was no bleeding or loss of consciousness. On the following day she complained of frontal headache and her temperature rose to 101°F. The head pain and fever responded promptly to acetylsalicylic acid, but recurred five days later, accompanied by pain in the left ear, swelling over the left side of the face and difficulty in opening her mouth.

*Examination.* The patient appeared to be acutely sick with flushed facies and a temperature of 104.8°F. There was a large reddened and tender swelling over the left side of the face extending from the zygoma to the lower margin of the mandible and from the tragus to the outer canthus of the eye. The mandible was displaced to the right. The trismus prevented adequate examination of the pharynx. The left tympanic membrane was reddened, somewhat full, and the landmarks were not discernible. A whitish exudate was present in the anterior sulcus, but there was no active discharge from the middle ear. A small abrasion of the anterior cartilaginous wall was noted. Pressure over the preauricular swelling, however, did not cause the appearance of any discharge in the canal. No postauricular swelling or mastoid tenderness was elicited; the cervical glands were enlarged.

*Laboratory data.* Blood count: 18,200 white blood cells per cubic millimeter, with 82 per cent segmented, and 4 per cent non-segmented polymorphonuclear leukocytes and 14 per cent lymphocytes; hemoglobin, 78 per cent. The urine findings were normal and the blood Wassermann reaction was negative. X-ray examination of the mastoid regions

revealed clouding of the pneumatic spaces in the left mastoid. The articular condyle on that side was displaced caudad and anteriorly, suggesting the presence of an effusion in the temporomandibular joint (fig. 1). This examination did not include a view with the mouth open. No abnormality in the zygoma was seen.

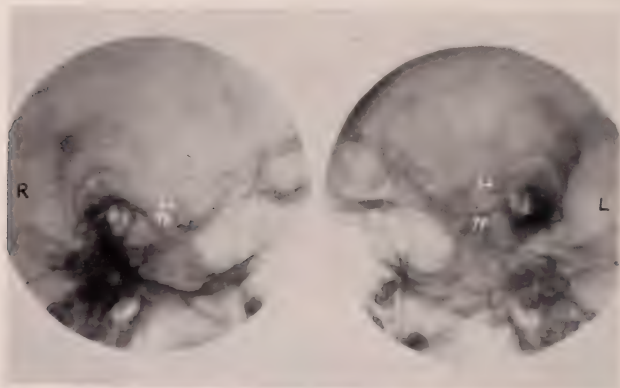


FIG. 1. The displacement of the articular condyle caudad and anteriorly is clearly visible on the left side. The condyle is in the normal position on the right.

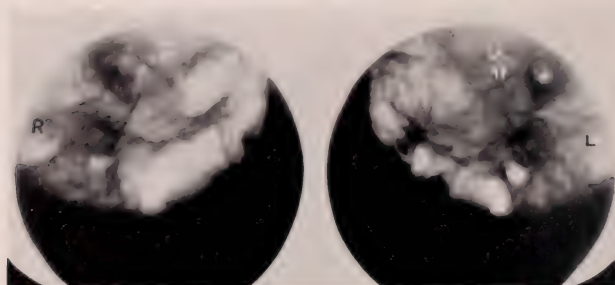


FIG. 2. Only slight displacement of the condyle is seen on the left side.

*Course.* The administration of penicillin and sulfadiazine combined with acetylsalicylic acid and local wet dressings as adjuvants adequately controlled the symptoms; the facial swelling and the trismus gradually subsided and the inflammation of the middle ear completely resolved. A second x-ray examination done five days after the first, however, showed a widening of the temporomandibular joint as the residuum. The patient made a complete recovery and was discharged 8 days after admission. A follow-up roentgen examination made 3½ months after the date of injury in the closed and open mouth positions disclosed almost complete restitution of the joint (fig. 2).



## DISCUSSION

The diagnostic problem in this case demanded the determination of the exact nature of the lesion causing the local swelling on the face. It was, however, most important to evaluate the clinical symptoms referable to the ear and to the face which appeared more or less simultaneously and to establish which of these pointed to the primary site of disease. It was, of course, essential to decide whether the otitic infection was primary and the facial swelling and the trismus secondary, as could be provoked by an acute mastoiditis with zygomatic cortical perforation, or whether the ear condition was secondary to the facial lesion, as is likely to occur in severe traumas to the temporomandibular joint region. The possibility of two distinct entities unrelated to one another and an otitis media with parotitis or suppurative adenitis also had to be considered. The short duration of the middle ear infection (6 days) particularly in the absence of a previous infection of the upper respiratory tract spoke against the diagnosis of acute mastoiditis with zygomatic perforation. On the other hand the trauma, though not severe, sustained 11 days prior to admission favored the diagnosis of a primary lesion about the jaw joint with secondary involvement of the ear. A parotitis could not be definitely ruled out.

The x-ray findings served well to establish the diagnosis by pointing to the existence of an effusion into the temporomandibular joint. It was concluded that the effusion in the joint was primary and the otitis media secondary. Of interest is the fact that x-ray diagnosis of such a condition has only rarely been reported in the past (3).

## SUMMARY

A case of traumatic effusion in the temporomandibular joint complicated by otitis media responding satisfactorily to sulfadiazine and penicillin therapy is reported. The importance of x-ray examination in establishing the diagnosis is emphasized. The diagnosis of this condition should always be kept in mind in the presence of a preauricular swelling even when complicated by an otitis media particularly when occurring following a trauma to the head.

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## CECOSTOMY FOR PROLONGED COLONIC ILEUS

H. E. LEITER, M.D. AND A. S. LYONS, M.D.

The case to be described serves to illustrate the value of cecostomy in a persistent and marked distention of the colon due to a paralytic ileus. Most instances of marked colonic distention of non-obstructive origin usually subside when the reflex cause of the paralytic ileus resolves or responds to the various non-surgical measures ordinarily employed for the relief of tympanites. This case, however, was the exception to the rule in its response to cecostomy drainage.

### CASE REPORT

*History.* (Adm. #536571) J. G., a man aged 67, entered the hospital for the second time on July 5, 1945. Two years previously he developed gross hematuria. Investigation at that time disclosed a transitional cell carcinoma of the urinary bladder. It was treated by cystoscopic fulguration and implantation of radon seeds into the base of the tumor. He felt well until a few days prior to the recent admission when the hematuria recurred. His general health was good and aside from some increased urinary frequency there were no other complaints.

*Examination.* The patient was thin but otherwise appeared well. He displayed no significant changes in his abdominal and chest cavities. Although his prostate was slightly enlarged, the base of the bladder was not infiltrated by tumor.

*Laboratory data.* The urine was grossly bloody. His blood count and blood pressure were within normal limits and the urea nitrogen of the blood was normal. Intravenous urography revealed an essentially normal upper urinary tract on both sides and cystoscopic examination disclosed a neoplasm involving the floor of the bladder.

*Operation.* (Dr. Hyman) On July 6, 1945 a suprapubic cystostomy was performed under spinal anesthesia and the entire tumor area was implanted with non-removable radon seeds.

*Post-operative course.* During the first twenty-four hours after operation he appeared comfortable and he drained an adequate amount of bloody urine. On the second day, the abdomen became markedly distended. This was accompanied by hiccoughs and vomiting. A Levin tube was passed and suction was applied. Fluids were administered parenterally. During the succeeding days almost 2000 cc. of bile stained fluid were aspirated from his stomach each day. The abdominal distention continued unabated. On the eighth post-operative day, x-rays of the abdomen were taken and these showed marked distention of the large bowel and also some distention of the small bowel. The picture was interpreted as showing a paralytic ileus. The use of various types of enemata, purgatives, prostigmine 1-2000 intramuscularly, and abdominal stupes failed to relieve the tympanites. The urea nitrogen of the blood, which was at first elevated, returned to normal and the chloride content of the blood remained at a level of 450 mg. per cent. He had a low grade fever which averaged 100.6°F. after an initial post-operative rise to 102°F.

On the twelfth post-operative day he began to develop an intense diarrhea. During the succeeding four days he eliminated approximately 60 oz. of liquid stool each day. Despite this, however, his abdominal distention continued to the same marked degree. The general condition deteriorated and he became disoriented. The pulse was rapid and at times poor in quality. At times there were episodes of auricular fibrillation. It became apparent that unless some drastic measure was utilized, a fatal outcome would be inevitable. On the eighteenth day after cystostomy an x-ray of the abdomen still revealed marked colonic distention. It was decided to perform a cecostomy in the hope of relieving the ileus. A tube cecostomy under local anesthesia through a McBurney incision was performed by Dr. Garlock on July 24, 1945.

Immediately after opening the cecum, a considerable amount of gas and liquid stool could be expressed from the colon with some diminution of the distention. The following day, the bowel was irrigated through the cecostomy tube with warm water. After forty-eight hours, the abdomen was much less distended and the general condition improved. By the fourth day, the Levin tube was removed and the patient began to take fluids and solid food by mouth. The diarrhea gradually decreased and after the eighth day the stools became constipated. His general condition improved gradually and the toxic psychosis subsided slowly. He was able to leave the hospital on August 26, 1945.

#### DISCUSSION

It has been the experience of surgeons that mechanical drainage of the small or large intestine is ineffectual in the treatment of adynamic ileus. Only a few coils are emptied and the distention remains. However, attempts to empty an atonic bowel by surgical means have been reported as successful in isolated instances. Cheever suggested in some cases the use of mechanical drainage of distended small intestinal loops by milking the contents out through a trocar. Rowley described a case of paralytic ileus secondary to an intraperitoneal abscess which showed rapid improvement after the threading of a tube through a cecostomy into the terminal ileum. Homans, although he did not necessarily advocate these procedures, indicated that even temporary relief of distention might so improve the intestinal blood supply that normal tone could be regained.

Thus, the marked and rapid favorable change in the present case following cecostomy may have been due to the improvement in the circulation of the bowel associated with withdrawal of retained fluid and gas which were contributing to the distention of atonic intestinal walls, thereby breaking the cycle of distention, stasis, and diminished circulation.

#### SUMMARY

A case of persistent post-operative paralytic ileus is described. The predominant distention was in the colon. Striking improvement followed the performance of a cecostomy after all other measures had failed.

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## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Oral Pencillin in the Treatment of Oral Lesions.* R. H. BRODSKY. Quart. Bull., Sea View Hosp., 8: 55, January, 1946.

This is a preliminary report discussing the advantages of a well-buffered oral penicillin tablet (in this case Per-Os-Cillin) therapy over the other methods of administering penicillin for certain specific conditions. Twenty-eight cases of oral disease are included. Eleven of 13 cases of periodontoclasia (pyorrhoea) responded well to the therapy. Five cases of Vincent's Angina responded promptly and satisfactorily. Ten miscellaneous cases including chronic maxillary sinusitis, alveolar abscess, periapical sinus, cellulitis, granuloma, periapical edema and post nasal drip displayed moderate to marked improvement after therapy.

*Medical Progress: Recent Progress in Surgery of Gastro-Intestinal Tract.* J. GARLOCK. New York Med., 2: 17, January, 1946.

The author in a brief summary discusses the recent advances in the surgical therapy of gastric and duodenal ulcer, cancer of the esophagus and stomach, ileitis, ulcerative colitis and cancer of the colon and rectum. Special emphasis is placed on early diagnosis, thorough pre-operative preparation and adequate post-operative care.

*Local Prophylaxis for Gonorrhea. An Improved Technic.* E. GRANET. Mil. Surg., 98: 25, January, 1946.

In the recent war, chemical prophylaxis utilizing a solution of mild silver protein in the urethra recommended by the American Neisserian Society was inadequate. By compression of the glans between thumb and index finger, the lumen of the contaminated anterior urethra was obliterated and the protargol solution was retained impotently in the urethra proximal to the presumably infected navicular urethra. To overcome this obvious mechanical fallacy, an improved technic was utilized at a Caribbean Naval Base. Following injection of the protargol, the penis was compressed at the corona between thumb and middle finger to retain the solution. The ball of the index finger was then placed over the meatus as a cap valve and compression on the urethra was slowly released, permitting the solution to descend to the anterior tip of the urethra. In a six month period, 10,470 chemical prophylactic treatments were administered; 34 men were infected despite prophylaxis. Incubation time averaged 10.5 days in 13 who used the new technic. This implies that the implanted gonococci were partially destroyed or at least vitiated by the treatment.

*Effect of Penicillin on Course of Early Syphilis.* W. LEIFER AND S. P. MARTIN. J. A. M. A. 130: 202, January, 1946.

Fifteen patients were treated with 50,000 or 100,000 units of penicillin for gonococcal urethritis while suffering from an unrecognized, concomitant early syphilitic infection. Penicillin appeared to prolong the incubation period of primary syphilis in 3 patients; the syphilitic lesions were suppressed and concealed in 8 patients; and a febrile Herxheimer reaction occurred on the day of penicillin therapy in 4 patients. In uncomplicated gonococcal urethritis the appearance of fever shortly after penicillin treatment calls for scrutiny of the patient for lesions of early syphilis. In all 15 cases the diagnosis of syphilis was

proved by demonstration of treponemas in the lesions, or by repeated positive serologic tests, in less than ninety days after penicillin was administered. On this basis, clinical and serologic observation for at least three months is recommended for all patients receiving penicillin for gonococcal urethritis.

*Studies on the Nature of Resistance of Gram-Negative Bacilli to Penicillin. Antagonistic and Enhancing Effects of Amino Acids.* G. SHWARTZMAN. J. Exper. Med., 83: 65, January, 1946.

The susceptibility of *E. coli* and *Salmonella* to penicillin is highest in a basal medium devoid of amino acids. Blood serum in certain concentrations, meat infusion broth, yeast extract, and casein hydrolysate interfere with the penicillin activity. The effect is apparently due to the antagonism of certain amino acids in the materials. Dicarboxyl-monamino acids (i.e. aspartic, glutamic, and hydroxyglutamic acids and asparagine) cystine, arginine, histidine, and hydroxyproline are capable of suppressing the effect of penicillin upon Gram-negative organisms. The antagonism of amino acids is not primarily related to their effect upon the rate of bacterial growth. It is suggested from the experiments detailed, that the antipenicillin activity is due to the effect of the amino acids upon bacterial metabolism. Prepassages in media of various concentrations of antagonistic amino acids alter the resistance of *E. coli* to penicillin. The changes are in inverse relation to the concentration of the antagonists. The antipenicillin activity of amino acids may be reversed significantly by dl-methionine. The substance, however, reverses only incompletely the antagonism of materials of mixed composition; i.e., casein hydrolysed, meat infusion broth, and serum. Upon addition of methionine, methionine sulfoxide, and threonine, there occurs a marked enhancement of penicillin susceptibility of broth cultures of *Brucella*, *Eberthella*, *Salmonella*, and *Shigella*. The enhancement is apparently due to the ability of this amino acid mixture to reverse effectively the action of the antagonists present in the cultures. Methionine is essential for the enhancement of penicillin susceptibility. Threonine and methionine sulfoxide facilitate the effect of methionine following a reciprocal quantitative relationship.

*Narcolepsy as a Psychogenic Symptom.* L. SPIEGEL AND C. P. OBERNDORF. Psychosom. Med., 8: 28, January, 1946.

Hospital observation of a patient who suffered from periods of uncontrollable sleep, demonstrated an hysterical hemiparesis and hemisensory syndrome and revealed that a regular succession of symptoms preceded the narcoleptic attacks. These consisted in characterological changes, aggravation of the functional neurological syndrome, vomiting, intense thirst and finally sleep. A narcoleptic attack could be induced at will by presenting certain significant material for the patient's consideration. The psychogenesis was found to lie in a conflict over incestuous experiences; the narcolepsy meant both the gratification of the incestuous wish and punishment for it, death. Cathartic ventilation of consciously withheld material resulted in a cure of the narcoleptic attacks. It is suggested that the activated incestuous wish was first expressed in circumscribed hysterical symptoms (hemiparesis, etc.) and finally in a narcoleptic attack. The narcolepsy in this case was considered to be a conversion symptom.

*Fixed Sulfathiazole Eruption of Unusual Distribution.* W. LEIFER. Arch. Dermat. & Syph., 53: 125, February, 1946.

A Negro soldier took sulfathiazole regularly for venereal prophylaxis. After two years an eruption appeared on the hard palate, tongue, lower lip and glans penis. The lesions were circumscribed, edematous, red and eroded. Black pigmentation was present about the lesions of the lip and penis. Small test doses of sulfadiazine and sulfathiazole caused a flare-up of the original sites of eruption and in addition there developed itching, rounded, red lesions of both palms and a vesicular dermatitis about a neck scar. The vesicular dermatitis of the neck resulted from sensitization by direct application of sulfathiazole to the laceration prior to suture; the other eruptive areas were sensitized hematogenously.



*The Radiologic Diagnosis of Ectopic Pregnancy.* R. H. MARSHAK. New York State J. Med., 46: 318, February, 1946.

Uterosalphingography to visualize tubal pregnancy has rarely been performed in this country. Case reports have appeared in the South American literature illustrating the application of this procedure. A report is presented of a patient on whom uterosalphingography was performed to determine the cause of uterine bleeding and an ectopic gestation accidentally visualized. The patient had had irregular periods with menometrorrhagia for three months. Curettage revealed proliferative endometrium and the Friedman test was negative. The hystrogram, therefore, was not done to visualize the ectopic pregnancy but, as stated previously, to further elucidate the cause of the bleeding. The x-ray revealed a filling defect one and one-half centimeters in diameter in the left tube. The diagnosis of tubal pregnancy was made and the patient explored. The procedure had no ill effects and since the diagnosis of ectopic pregnancy can be difficult especially in unruptured cases further patients should be studied to determine the desirability of doing uterosalphingograms for suspected ectopic pregnancies.

*The Calculation of Dose from Point and Linear Sources of Radium.* S. M. SILVERSTONE. Am. J. Roentgenol., 55: 203, February, 1946.

The following formulas have been derived for the calculation of dose from point and linear sources of radium in terms of the gamma roentgen:

1. The point source formula

$$D = \frac{M \times t \times C \times S}{h^2}$$

2. The linear source formula

$$D = \frac{M \times t}{L \times h} \times \left[ f\left(\frac{L-a}{h}\right) + f\left(\frac{a}{h}\right) \right] \times S$$

A few useful simplifications of these formulas have also been derived. The various factors concerned are given in the form of tables. The significance of the various factors is discussed. The limitations of accuracy of the formulas were analyzed. Several examples were given to illustrate the application of the formulas.

*Tympanic Plexus Tinnitus versus Reflex Dental Tinnitus.* R. H. BRODSKY. New York J. Dent., 16: 108, March, 1946.

The problem of tinnitus of dental origin occurs with sufficient frequency to make requisite some knowledge of certain forms of oral pathology and abnormal occlusion as relating to this condition. It has been demonstrated that: (1) teeth and bite may produce tinnitus by reflex irritation of ganglia leading to the tympanic plexus; (2) that primary disturbance of the tympanic plexus is probably responsible, in a large measure, for that tinnitus which is associated with the various syndromes of true deafness, vertigo and tinnitus; and (3) where dental pathology can be excluded, and where there is deafness and a history of vertigo, the subsequent course of treatment provided suggestive evidence that denervation (stripping of the tympanic plexus by the otologic surgeon might effect relief.

*Organic Thinking Difficulty.* I. S. FREIMAN AND P. V. LEMKAU. J. Nerv. & Ment. Dis., 103: 239, March, 1946.

A case of brain damage resulting in thinking difficulty of organic type is presented. Tests which are easily available for the demonstration of the thinking disorder are described. The patient was unable to integrate facts into general concepts and unable to apply a general principle to a new set of facts, though he had good recall of factual information. Such cases may be misdiagnosed as malingering and soldiers thereby treated unfairly.

*Penetration of Penicillin into Foci of Infection.* I. E. GERBER, G. SHWARTZMAN AND G. BAEHR. J. A. M. A., 130: 761, March, 1946.

The intermittent intramuscular injections of large doses of penicillin at three hour intervals seem in general to be more effective in the control of bacteremia and of local infections than continuous intravenous administration of the same total daily amount. The intramuscular administration of penicillin in divided doses has the distinct advantage of producing a higher peak level in the blood intermittently throughout the day, thereby favoring penetration of penicillin into vegetations of acute and subacute bacterial endocarditis and into suppurative thrombophlebitis or other primary sites of bacteremia. To assure penetration of adequate amounts of penicillin into primary foci responsible for bacteremia (i.e. vegetations, thrombophlebitis), additional massive "booster doses" should be five or six times the routine intramuscular dosage which has produced blood levels sufficient to clear the blood of bacteria. Subacute bacterial endocarditis and other chronic infections due to organisms of relatively high penicillin resistance are more advantageously treated with massive doses at frequent intervals throughout the day (every three hours). The minimum duration of therapy of subacute bacterial endocarditis, should be five weeks. In purely localized infections with highly resistant organisms, such as Actinomyces, penicillin is best concentrated in a few massive intramuscular doses each day in order to favor penetration by means of exceptionally high peak levels and, if possible, also administered directly into the infected area.

*The Fetal Mortality in Women during the Prediabetic Period.* J. HERZSTEIN AND H. DOLGER. Am. J. Obst. & Gynec., 51: 420, March, 1946.

Two hundred diabetic women gave birth to 626 children during their prediabetic years. The total infant fatality rate (stillbirths and deaths within ten days after birth), was 6.1 per cent. The corresponding rate for nondiabetic women as given by others ranged from 2 to 6 per cent. The fetal fatality rate for the first five years preceding the onset of recognized diabetes was 15.4 per cent. The first five-year prediabetic period revealed an increased fetal and neonatal mortality but the preceding fifteen years was not characterized by such a tendency. The total rate for the entire twenty-year prediabetic period did not differ significantly from normal. The rate for the total twenty-year prediabetic period was about the same as that for the period of over twenty years, namely, 6 per cent. The stillbirth and neonatal fatality rate among women who were destined to require insulin was not higher than among those who developed mild diabetes.

*Calcium in Gastric Mucus.* F. HOLLANDER AND F. U. LAUBER. Federation Proc., 5: 1 March, 1946.

Mucus was collected from dogs' Heidenhain pouches by contact stimulation with emulsions of eugenol (5 per cent) and mustard oil (1 per cent). Calcium content, electrometric pH, and a qualitative evaluation of viscosity were noted for each specimen. The difference between the mean calcium values for the eugenol and mustard oil-stimulated material is without statistical significance. The pH's of the secretions were invariably above 7.4 and correlate poorly with calcium concentration. Serum calcium values were obtained in some instances and were always greater than the simultaneous mucus values. Treatment with 0.1 N HCl *in vitro* extracts all of the calcium from the insoluble portion of the mucus.

*Neutralization of Inhibition of Tumor Growth.* J. C. KERESZTESY, D. LASZLO AND C. LEUCHTENBERGER. Cancer Research, 6: 128, March, 1946.

By adapting a method that detects inhibitors of tumor growth it is possible to demonstrate that the action of inhibitors can be effectively neutralized by both structurally related or unrelated substances. Neutralization by approximately equal amounts of inhibitor and antagonist was observed in the inositol: *p*-amino-benzoic acid, inositol: pyridozine, and *d*-desthiobiotin: *d*-biotin experiments. Thiamin, niacinamide, *o*- and *m*-

aminobenzoic acid, and leucopterin were slightly active, if at all, in counteracting the inhibition caused by inositol. Interference could be detected when larger doses of some of these substances were given. While both *d*-desthiobiotin and an avidin concentrate were effective inhibitors of tumor growth, neutralization occurred when these two materials were tested for antagonism. Impurities in the avidin concentrate may be responsible for this interference.

*Maintenance of Therapeutic Blood Concentrations of Penicillin for Twenty-Four Hours Following Single Injections of Penicillin-Beeswax-Peanut Oil Mixtures.* W. M. M. KIRBY, S. P. MARTIN, W. LEIFER AND J. M. KINSMAN. *J. Lab. & Clin. Med.*, 31: 313, March, 1946.

Effective therapeutic concentrations of penicillin are maintained in the blood stream for twenty-four hours or longer following single subcutaneous injections of 600,000 units of penicillin in beeswax-peanut oil. Results following intramuscular injections are somewhat less satisfactory than with the subcutaneous route.

*Thyrotoxic and Thyrotropic Exophthalmos from the Ophthalmologist's Viewpoint.* J. LAVAL. *Eye, Ear, Nose & Throat Monthly*, 25, 139, March, 1946.

The case histories of three different types of exophthalmos due to thyroid dysfunction were presented. The first was of a woman with typical Graves' disease and exophthalmos which was not effected by thyroidectomy, (thyrotoxic exophthalmos). The second patient was a young man with Graves' disease whose exophthalmos became malignant following thyroidectomy, necessitating a Naffziger operation for both orbits. The visual result was perfect with 20/20 for each eye but with a resultant diplopia for distance for which muscle surgery will be necessary, (secondary thyrotropic exophthalmos). The third case was a male in the middle fifties who developed a unilateral exophthalmos five years after removal of the left kidney for hypernephroma. Operation on the orbit of the protruding globe showed no tumor but rather typical changes in the rectus muscles indicative of primary thyrotropic exophthalmos.

*Glioma of the Optic Nerve.* M. MANNHEIMER. *Am. J. Ophth.*, 29: 3, March, 1946.

To the 300 cases of glioma of the optic nerve so far published another one in a colored girl 8 years of age is added. The history and symptomatology are given, stressing the importance of the x-ray picture of the skull. The affected optic foramen is twice as large as the other one, indicating that the nerve was involved both within the orbit and the skull. Thus, the therapy of choice is an intracranial nerve resection almost up to the unaffected chiasm, followed thirty-two days later by an enucleation and an intraorbital extirpation of the nerve. The globe could not be preserved, its posterior pole having been involved as diagnosed from the earlier ophthalmoscopic picture. The tumor being entirely confined to the nerve was microscopically verified as glioma. The prognosis is to be regarded as favorable as gliomas to not metastasize. The differential diagnosis, origin and growth of the gliomas and their occurrence and histology are discussed.

*Functional Paroxysmal Auricular Fibrillation.* A. M. MASTER AND H. EICHERT. *Am. J. M. Sc.*, 211: 336, March, 1946.

Paroxysmal auricular fibrillation, unassociated with organic heart disease is not infrequent. Emotional and mental strain and excessive use of tobacco and coffee are factors in its production. Palpitation of the heart is the chief presenting symptom. The "rapid" heart is occasionally noticed but the irregular heart action is rarely observed by the patient. Digitalis should be administered if heart failure is present or impending. Potassium acetate may be successful when quinidine sulphate is not available. Before recourse is made to any drug, other methods for stopping an attack should be essayed. Reassurance, complete rest, certain positions of the body, carotid sinus or ocular pressure are first to be tried. The paroxysms may be prevented by avoiding excessive exertion, mental and physical fatigue, lack of sleep, excessive use of tobacco and coffee, and gastric disturbances.

## SPONTANEOUS RUPTURE OF A PAPILLARY MUSCLE OF THE HEART

A REPORT OF THREE CASES AND A REVIEW OF THE LITERATURE<sup>1</sup>

SELVAN DAVISON, M.D.

Spontaneous rupture of a papillary muscle of the heart is a rarity. Even less common must be the antemortem diagnosis of this condition, for no such instance has been found in the literature. The opportunity to observe a case of this kind and to establish its correct clinical diagnosis accordingly has prompted this report.

In 1935 Stevenson and Turner (1) reviewed the literature of this subject and found 19 post mortem case reports, to which they added one of their own. Six additional instances have been recorded since their review (2-6). The purpose of the present report is to present three additional cases and to discuss the etiological and clinical features. (Two further cases, numbers 27 and 28, have been included in Table I, and were made available through the courtesy of Dr. John Martin Askey of Los Angeles, California. These cases are to be published by Dr. Askey as a separate report.)

### CASE REPORTS

*Case 1. History.* (Adm. # 560806—Medical service of Dr. George Baehr) P. S., a 55 year old white male, employed as an elevator operator, was admitted to The Mount Sinai Hospital on February 18, 1947. He had been well and active until four days before admission, when he began to complain of easy fatigability and a sense of heaviness in his legs. However, he continued his usual activities. Two days prior to admission he had noted the sudden onset of pressing, substernal pain with occasional radiation to the region of the left scapula. The pain subsided within half an hour only to recur twice more, and lasted half an hour each time. On the day before hospitalization he was dyspneic and developed a cough productive of small amounts of gray sputum; while substernal pain returned whenever he arose from bed. He was then taken to the hospital.

The patient had known of mild hypertension, discovered accidentally two years before. He had had recurrent attacks of "rheumatism" for the past twenty-seven years. Symptoms of peptic ulcer occurred thirteen years ago.

*Examination.* The patient was well developed, well nourished, but markedly dyspneic, orthopneic, cyanotic, and coughing frequently. The retinal arteries were thin and resembled silver wire. The chest was emphysematous; coarse rales were audible at both bases, especially on the right. The maximum cardiac impulse was located in the fifth interspace at the midclavicular line. The second aortic sound was louder than the second pulmonic sound. A blowing systolic murmur was heard over the entire precordium, with accentuation over the mitral area. A short diastolic blow was audible at the mitral area. Distinct gallop rhythm was present, and the sounds were of poor quality. The ventricular and pulse rates were 140 per minute. The blood pressure was 80 systolic and 65 diastolic. There was moderate thickening of brachial and radial arteries. The nail beds were cya-

<sup>1</sup> From the Medical Services, and the Laboratories (Division of Pathology) of The Mount Sinai Hospital, New York.



notic. The temperature was 101.8 degrees Fahrenheit, and the respiratory rate averaged 54 per minute.

A diagnosis of ruptured papillary muscle of the heart, secondary to coronary artery occlusion and myocardial infarction was entertained.

*Course.* The patient was placed in an oxygen tent and treated with sedation, aminophylline, dicoumarol, mercurhydrin; and his intake of fluid was limited to 1500 c.c. daily.

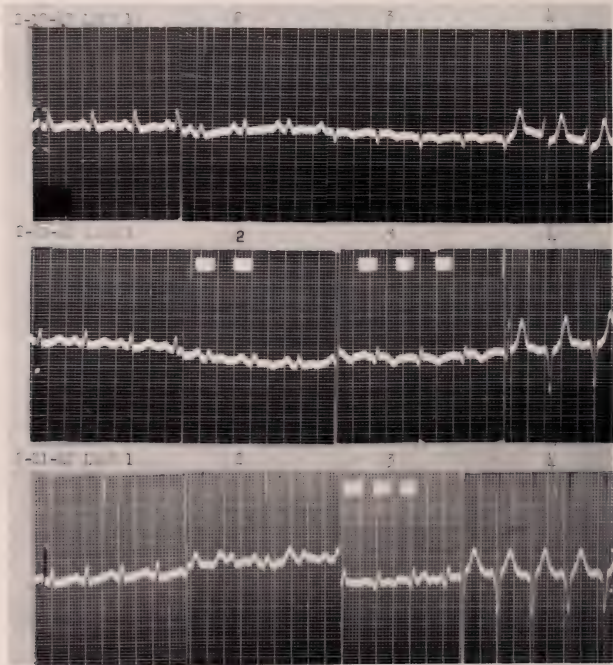


FIG. 1. February 19, 1947—Sinus tachycardia 110 per minute. Left axis deviation. RST-3 slightly elevated. RST-1, 2, and 4 depressed. T-3 inverted. T-2 low. February 20, 1947 T-2 diphasic; T-3 deeper inverted; R in CF-4 absent. February 21, 1947 Sinus tachycardia with rate 145. Interpretation: Recent coronary occlusion with posterior wall infarction.

Digitalis Nativelle was begun two days after admission and maintained in a dosage of 2 cat units of the leaf. Hykinone was given by intramuscular injection on the fifth day in view of the sudden decrease in prothrombin time index to 28 per cent. Penicillin was administered intramuscularly from the time of admission for it was felt that left lower lobe pneumonia might be present concomitantly. Despite treatment the patient never rallied to any extent. The blood pressure never rose above 106 mm. systolic and 84 mm. diastolic. Coarse, bubbling rales were heard as far as the midscapular region, bilaterally. The



gallop rhythm and the harsh systolic apical murmur persisted, and heart sounds remained poor. The liver edge slowly extended to a point 2 fingerbreadths below the costal margin. However, no other clinical evidence of venous engorgement appeared. The pulse rate continued to be rapid and in the neighborhood of 140 per minute. The patient deteriorated steadily and died on his eighth hospital day.

*Laboratory data.* The white blood count was 11,650, rising to 21,000 with 92 per cent polymorphonuclear leucocytes. The hemoglobin (Sahli) was 101 per cent and the red blood count was 4,950,000 per cu. mm. Erythrocyte sedimentation rate (Westergren) was 20



FIG. 2

mm. per hour. Urinalysis revealed a specific gravity of 1.026; faint trace of albumin; sugar negative; one to two leucocytes and a few hyaline and granular casts were found per low power field microscopically.

Serial electrocardiograms disclosed alterations as shown in the accompanying E.C.G. chart (fig. 1).

*Post mortem findings. Gross.* The heart was moderately enlarged and weighed 373 grams. The middle of the posterior wall of the left ventricle contained a softened area having a diameter of about 3 cm. The posterior papillary muscle was trifid. The anterior and posterior processes were intact, soft and yellow. The middle process was soft and yellowish; it was ruptured transversely through its central portion (fig. 2). The anterior

papillary muscle was hypertrophied, firm and red-brown. In the posterior wall of the left ventricle, adjacent to the posterior papillary muscle was a large, soft area about 5 cm. in diameter, extending almost to the apex and involving the entire thickness of the wall. Within this soft area there were multiple, varying-sized, sharply circumscribed, yellow patches with thin, hyperemic margins. These alternated with brown, thin bands of muscle. The anterior wall of the left ventricle was the seat of a dense, grayish-white zone about 4 cm. in diameter. The myocardium of the left ventricle was thickened throughout, measuring up to 2 cm. in width. The main stem and the two major branches of the left anterior descending artery exhibited severe arteriosclerotic thickening, which greatly narrowed the lumen for a distance of 2 cm. The circumflex branch of the left coronary artery showed moderate, severe, calcific arteriosclerosis, with moderate to marked narrowing of the lumen. About 2.5 cm. distal from the origin of the margo obtusa branch, a bright red, soft thrombus occluded the lumen for several millimetres. The mitral leaflets and chordae tendineae showed no significant change. The remaining valves were normal. The wall of the right ventricle was moderately hypertrophied. The aorta was the seat of a considerable degree of arteriosclerosis.

*Microscopic observations.* Sections from the posterior wall of the left ventricle disclosed fresh infarction. In the posterior papillary muscle there were large patches of freshly necrotic and hemorrhagic myocardial tissue without significant cellular reaction.

*Summary of the anatomical findings.* Coronary arteriosclerosis, severe, with recent thrombotic occlusion of circumflex branch, left coronary artery. Acute myocardial infarction, posterior wall, left ventricle; posterior papillary muscle, with rupture of its middle segment; organized occlusion of left anterior descending artery with healed infarct, anterior wall, left ventricle; hypertrophy of heart, moderate; confluent bronchopneumonia, severe, bilateral.

*Comment.* Because of fever and an apical murmur this patient was suspected of having subacute bacterial endocarditis and was referred to the hospital. The referring physician had offered this diagnosis because the murmur had appeared recently. When the patient was examined in the reception ward of the hospital, however, it was felt in view of the recurrent substernal pain and history of hypertension that acute myocardial infarction had developed. The presence of a rough, harsh, systolic murmur, and a questionable diastolic murmur, heard best at the mitral area, associated with the picture of myocardial infarction, strongly suggested the possibility of recently ruptured papillary muscle of the left ventricle.

*Case 2. History.* (Adm. # 463668—Medical service of Dr. B. S. Oppenheimer) A. S., a 69-year-old, white housewife was admitted on October 9, 1940. She had known of hypertension for 15 years (systolic pressure between 170–190 mm. Hg), and had experienced attacks of precordial pain, relieved by nitroglycerine. For 5 years she had had hay fever and bronchial asthma. The asthmatic attacks had increased in frequency and severity for several days before admission and had necessitated daily injections of adrenalin. For 36 hours prior to admission she had been in status asthmaticus. The systolic blood pressure, measured at home, was 130 mm. of Hg. The patient frequently had had cough productive of frothy sputum.

*Examination.* The patient was a well developed and well nourished white woman in severe respiratory distress, cyanotic with an underlying pallor. Her skin was cold. Dorsal kyphosis and evidence of emphysema were marked. Crackling rales were audible at the bases and rhonchi were noted throughout both lungs. The heart was moderately enlarged to the left. A systolic murmur was heard at the apex. The second aortic sound was louder than the second pulmonic. The blood pressure was 130 mm. systolic and 90 mm. diastolic. Evidence of moderate arteriosclerosis was found.

*Course.* Aminophyllin and oxygen brought no relief. Four hours after admission, evidence of shock suddenly appeared, and the patient died.

*Post mortem findings. Gross.* The heart weighed 135 grams. The wall of the left ventricle was hypertrophied, and the chamber dilated. The anterior portion of the septum toward the apex was white, opaque and somewhat thin. This fibrotic area occupied the anterior-inferior part of the interventricular septum and extended for a short distance into the anterior wall of the left ventricle. At the extreme apex, the myocardium was thinner, and a small, bulging area was formed in which lay a mural thrombus measuring  $3 \times 2 \times 0.8$  cm. The lateral wall of the left ventricle in the region of the margo obtusa branch of the left coronary artery was mottled, hemorrhagic, yellow and brown. The middle portion of the anterior papillary muscle was the site of rupture. The torn surfaces were covered with adherent blood clot and the involved area appeared soft and friable. There was an accessory left coronary artery which continued as the left circumflex artery, and this contained a fresh obliterating thrombus, originating 2.5 cm. from the ostium and extending for 0.5 cm. The margo obtusa branch arose just beyond this point and was conspicuously and eccentrically thickened throughout, with severe stenosis of its lumen. The remainder of the coronary vessels showed marked thickening with narrowing generally, and almost complete obliteration of the lumen at one point of the posterior longitudinal sulcus branch of the right coronary artery. The chordae tendineae inserted in web-like fashion into slightly thickened mitral valve leaflets. There was a recent focal hemorrhage within the posterior leaflet. The leaflets of the tricuspid valve were thin and smooth and contained several small, discrete, recent hemorrhages. The wall of the right ventricle was thickened and its cavity dilated. The aorta was moderately arteriosclerotic in the thoracic and markedly so in the abdominal portion.

*Summary of the anatomical findings.* Arteriosclerosis of coronary arteries with marked narrowing anterior descending branch of left coronary artery and right circumflex artery. Organized, recanalized, thrombotic occlusion ramus margo obtusus, posterior longitudinal sulcus. Myofibrosis with atrophy anterior wall left ventricle and secondary mural thrombus. Recent thrombotic occlusion left circumflex artery. Acute massive myomalacia of lateral wall, left ventricle and papillary muscles, with recent spontaneous rupture of anterior papillary muscle.

*Comment.* It was realized at the time of the patient's final collapse that she had suffered an acute myocardial infarction. An electrocardiogram could not be obtained. In retrospect, one feels that the physical findings, together with the blood pressure of only 130 systolic mm. of Hg, in the face of a past history of hypertension, should have suggested the diagnosis of acute myocardial infarction upon admission. In view of the rapidity of the course it is probable that the rupture of the papillary muscle was an impossible diagnosis.

*Case 3. History.* (Adm. # 454281—Medical service of Dr. George Baehr) K. T. This 63 year old, white male, a tailor, was admitted to The Mount Sinai Hospital on March 26, 1940. He had suffered from intermittent claudication of his extremities for the previous 2 years, and had known of hypertension for the same period. Three days before admission, while sitting quietly, he experienced a severe cutting pain in the popliteal area, which radiated down the leg to the foot and great toe, followed several hours later by blueness and coldness of the latter.

*Examination.* The blood pressure was 128 systolic, 68 diastolic, mm. of Hg in each arm. A soft systolic murmur was heard at the base of the heart. The anterior aspect of the right foot was red, tender, and swollen. Only the right femoral pulse was palpable in either lower extremity. The right calf was tender; the right hallux was purple and cold and there was a line of demarcation 15 cms. proximal to the tip.

*Laboratory data.* Hemoglobin 85 per cent (Sahli); white blood cells 19,000 per cu. mm. with 71 per cent polymorphonuclear leukocytes and 16 per cent non-segmented forms.

Urine: Trace of albumin; specific gravity 1.026. Blood urea nitrogen was 9 mgm. per cent and the fasting blood sugar was 115 mgm. per cent. The blood Wassermann reaction was negative.

*Course.* Conservative measures were adopted in an attempt to save the limb. However, the area of demarcation continued to spread and involved the other toes. On the third day in hospital, the patient suddenly showed signs of profound collapse accompanied by sudden drop in blood pressure. An electrocardiogram showed the pattern of posterior wall infarction. Pulmonary edema set in, the temperature rose to 102.8 degrees Fahrenheit, respiratory distress increased and death occurred on the following day, four days after entry.

*Postmortem findings. Gross.* The heart weighed 425 grams. The left ventricle was hypertrophied and dilated. The posterior wall of the left ventricle was soft. On section, the muscle appeared mottled with yellow areas scattered through the dark brown muscle. The posterior papillary muscle of the left ventricle was completely ruptured through its upper third. The torn surfaces of the muscle were irregular and covered by adherent blood clot. The distal torn surface showed a triangular soft yellow area. In addition the torn surface was smooth although irregular in contour and was covered by a layer of fibrin. Both leaflets of the mitral valve disclosed marked arteriosclerotic thickening. The free margins were thickened and puckered. The chordae tendineae were somewhat thickened but not fused. The right coronary ostium was markedly narrowed by the surrounding aortic arteriosclerosis. Four cms. distal to its origin, the lumen of the right coronary artery was completely occluded for a distance of three cms. by a fresh dark red soft adherent thrombus. The right ventricle was dilated and hypertrophied. The aorta exhibited marked arteriosclerosis; and there was an adherent thrombus in the lower seven cms. partially occluding the lumen, which extended into the right and left iliac arteries with almost complete obstruction of their lumina.

*Summary of anatomic findings.* Coronary arteriosclerosis with narrowing of lumina; acute thrombotic occlusion of right coronary artery; acute myomalacia, posterior wall of left ventricle with spontaneous rupture of posterior papillary muscle of left ventricle.

*Comment.* Subsequent to the disclosure of a ruptured papillary muscle, it was recalled by one observer that coincident with the appearance of shock on the third day, the systolic murmur which had been described on admission became longer in duration, of higher pitch and was then best heard over the cardiac apex. Such sudden change in the murmur with maximum audibility at the apex, along with the diagnosis of sudden acute myocardial infarction, and appearance of sudden and complete collapse, could have suggested the possibility of ruptured papillary muscle.

#### DISCUSSION

*Review of the literature.* Stevenson and Turner (1) reviewed the literature up to 1935. The following table summarizes the 20 cases reviewed by them; six further cases published since then; the three presented in this paper; and the two by personal communication from Dr. Askey.

*Incidence.* Stevenson and Turner found 2 cases in 6000 autopsies at the Baltimore City Hospital, and no such instance in 14,000 at the Johns Hopkins Hospital. The present report of three cases were found in almost 14,000 autopsies performed at The Mount Sinai Hospital in New York City.

*Pathogenesis.* In 1824 Bertin (7) reported a case of rupture of a papillary muscle of the right ventricle, allegedly due to tuberculous vegetations. In 1865

TABLE I

CASE NO.	AUTHOR	SEX	AGE	RUPTURED PAPILLARY MUSCLE	PATHOLOGY	SYMPTOMS
1	Mérot	M	40	Left ventricle.	Aneurysm of the aorta. Enlarged heart.	Palpitations, suffocation, and back pain while lifting heavy weight. Bedridden 20 months before death.
2	Corvisart	M	30	Left ventricle.	Heart not enlarged. Fresh clot on torn ends of muscles.	Dyspnea and hemoptysis. Edema and irregular pulse. Death in 9 days.
3	Bertin	F	22	Right ventricle.	Tuberculosis with vegetations on muscle and valves and chordae tendineae.	Severe coughing. Terminal pulmonary tuberculosis. Death in 18 hours.
4	Nicod	F	?	Left ventricle, anterior and posterior.		Death in 2 weeks after recurrent severe dyspnea and palpitations.
5	Spanton	F	23	Right ventricle.	Puerperal sepsis with vegetations on valves and chordae tendineae.	Loud systolic murmur at base. Death 7 weeks postpartum after peritonitis and pneumonia.
6	Le Piéz	F	74	Left ventricle.	Infarction and softening of the myocardium. Firm, grey clots in the smaller coronary arteries and in some of the larger.	Sudden syncope. Then squeezing chest pain. Irregular pulse and murmurs (not described).
7	Osler	M	70	Left posterior.	Calcified coronary vessels. Large coronary orifices.	Irregular pulse. Loud, rough systolic murmur at the apex.
8	Dévé	F	77	Left posterior.	Normal coronary arteries.	Dyspnea and weakness for 3 days. Sudden angina and death in 45 minutes. No murmurs heard.
9	Dennig	M	49	Left posterior.	Thrombus in right coronary artery.	Sudden increased angina, pneumonia, empyema and pericarditis. On the 33rd day, pain, nausea, cyanosis, irregular pulse and death in 7 hours. No murmurs heard.
10	Teacher	M	64	Left ventricle.	Extreme arteriosclerosis of coronary vessels. Patchy infarction of papillary muscle.	After 1 week's complaint of peculiar chest sensations there was sudden coma and death in 10 minutes. No murmurs heard.
11	Wankel	M	58	Left anterior.	Thrombus first branch of left circumflex artery. Heart enlarged.	3 years dyspnea and palpitations and then sudden angina, irregular pulse, apical whistling systolic sound, pulmonary edema and death in 24 hours.
12	Spalding and Von Glahn	M	31	Left posterior.	Syphilitic aortitis. Treponema pallidum in the heart muscle.	Sudden collapse and death. Murmurs of aortic insufficiency.
13	Fischer	M	62	Left posterior.	Thrombus in anterior descending branch of left, and distal end of right coronary artery.	Sudden severe angina; heart failure. Death after 10 months in hospital. To and fro murmur at the apex.
14	Von Glahn and Horowitz	F	69	Left posterior.	Posterior wall infarction. Extreme arteriosclerosis of coronary arteries. Thrombus in right circumflex artery.	Severe angina and heart failure. Sudden hemiplegia and death in 21 days after onset. Faint high-pitched systolic murmur in precordium and left axilla.



TABLE I—Continued

CASE No.	AUTHOR	SEX	AGE	RUPTURED PAPILLARY MUSCLE	PATHOLOGY	SYMPTOMS
15	Wagner	M	63	Left posterior.	Thrombus in anterior descending branch of left anterior coronary artery near its origin.	Severe angina. Death in 2 days. Loud apical diastolic murmur.
16	Wagner	M	65	Left anterior.	Myocardial infarction. Arteriosclerosis of coronary arteries. Thrombus in right coronary artery.	2 years known heart disease. Sudden angina. 2 weeks afterward, repeated pain, shock and death in 45 minutes. Loud noises over precordium not heard before.
17	Klein	M	58	Left posterior.	Coronary arteriosclerosis. Thrombus in posterior descending branch of right coronary artery. Posterior wall infarction.	Sudden death. No murmurs recorded.
18	Jetzler and Finkeldey	M	58	Left posterior.	Foci necrosis in anterior papillary muscle. Extreme arteriosclerosis of coronary arteries. Thrombus in distal end right coronary artery.	Sudden angina. After 15 days, recurrent pain and death in 36 hours. To and fro murmur at the apex.
19	Voigt	M	59	Left posterior.	Coronary arteriosclerosis. Thrombus in circumflex branch of left coronary artery. Posterior wall infarction.	Sudden angina and dyspnea; death in 3 days. Soft apical systolic murmur.
20	Stevenson and Turner	F	52	Left anterior.	Thrombus posterior descending branch of left circumflex artery. Myocardial infarction, including the anterior papillary muscle. Severe coronary arteriosclerosis.	Sudden dyspnea, coma and death, while in bed. Death in 15 minutes.
21	Hausen-Faure and Hasen-jäger	M	52	Left anterior.	Marked arteriosclerosis. Occlusion one descending branch left coronary artery.	Soft apical systolic murmur prior to acute episode. Two days chest pain radiating left arm, followed by sudden collapse and death in 21 hours. No further murmur described.
22	Hausen-Faure and Hasen-jäger	M	68	Left posterior.	Occlusion circumflex branch of left coronary artery.	Ten days chest pain radiating to left arm. Pain suddenly increased in intensity, cyanosis appeared and the patient died 9 hours afterward. A systolic murmur at the apex was described.
23	Lipscomb	M	64	Left posterior.	Arteriosclerosis of coronary arteries without narrowing. Petchial pericardial hemorrhages. Torn ends of muscle hemorrhagic. No coronary occlusion or myomalacia.	Sudden substernal anginal pain and shock. On 3rd day pain increased. Loud apical systolic murmur on 5th day. Increased pain and death on 9th day.
24	Moragues	M	52	Left posterior.	Anterior wall myocardial infarction. Thrombus anterior descending branch left coronary artery.	Sudden coma and convulsions. Recovered consciousness and noted chest fulness and dyspnea. Died en route to hospital.

TABLE I—*Concluded*

CASE NO.	AUTHOR	SEX	AGE	RUPTURED PAPILLARY MUSCLE	PATHOLOGY	SYMPTOMS
25	Lowry and Burn	M	68	Left posterior.	Posterior wall infarction. Thrombi in all branches left coronary artery.	Sudden chest constriction and severe angina and collapse. Had hemoptysis for 1 week previously. Loud noise called a friction rub to left of sternum in 4th interspace. Died same day.
26	"Cabot Case"	M	51	Left posterior.	Healed infarction posterior wall left ventricle. The remains of the left posterior papillary muscle, a thin fibrous band, arose from the infarcted area, and retracted and made incompetent the posterior leaflet of the mitral valve. Old thrombus right coronary artery, and recent thrombus proximal to this point.	Epigastric pain, chills and fever 5 weeks previously. Developed congestive failure. Went downhill and died 13 days after entering hospital. Grade 4 "wood sawing" systolic murmur and high pitched diastolic murmur at apex.
27	Askey, John Martin (Los Angeles)	M	57	Left anterior.	Polyarteritis nodosa involving heart, liver and bladder, principally multiple acute infarctions of the myocardium. Acute degeneration and inflammation of the muscle, including the papillary. Coronary arteries slightly arteriosclerotic with no thromboses.	Extensive gluteal and iliopsoas abscesses. Suddenly developed pulmonary edema and a harsh systolic murmur at the apex. Died 24 hours later.
28	Askey	M	76	Left anterior.	Large myocardial infarction. Left anterior descending branch left coronary artery arteriosclerotic but not narrowed. Branch to anterior surface from circumflex artery almost occluded by arteriosclerosis. No thrombi described.	Had acute suppurative cholecystitis with ruptured gall bladder. Developed pulmonary edema and shock. An electrocardiogram revealed a right bundle branch block. No murmurs are described. Death in 4 days.
29	Davison	M	55	Left posterior.		
30	Davison	M	63	Left posterior.		
31	Davison	F	69	Left anterior.		

Spanton (8), reported a case of puerperal sepsis with resultant bacterial endocarditis and complete tearing of a right ventricular papillary muscle. In 1921, Spalding and Von Glahn (9) presented a case of left ventricular posterior papillary muscle rupture following syphilitic cardiovascular disease, with aortitis and aortic insufficiency. *Treponema pallidum* was found in the heart. Mérat (10) in 1803, in what seems to be the first published case of ruptured papillary muscle, also mentions an aneurysm of the aorta being found. It seems altogether possible that his case may also have been one of syphilitic cardiovascular disease.

(An historical note is of interest at this point, when citing the report of Mérat. As Stevenson and Turner (1) pointed out, Corvisart, (26) except in one other

instance, has always been credited with publishing the first reported case. They again mention the paper of Mérat. Of further interest, however, is that in reading the latter work, one finds that Corvisart himself discusses Mérat's case.)

Except for the cases just cited, instances of spontaneous rupture of a papillary muscle have all been associated with coronary arteriosclerosis.

Respective papillary muscle involvement is as shown in Table II.

Stevenson and Turner (1) state that Dennig (11) in 1909 first stressed the etiologic relationship between coronary occlusion and rupture of papillary muscles. In reviewing the literature one finds that this statement is not quite true. For example, Le Pièz, (12) in his thesis, written in 1873, stressed the findings of coronary artery disease and the presence of firm grey clots; he wrote that these lesions caused infarction, softening, and rupture of the papillary muscle. The paper of Le Pièz alone provides sufficient evidence that the importance of coronary artery involvement was understood long before Dennig published his case.

Previous studies of the cases reported have shown that generally rupture of the anterior papillary muscle of the left ventricle is associated with occlusion of either the anterior descending branch of the left coronary artery or of the first

TABLE II

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|----|--|
| 1. | 16 cases—left ventricular papillary muscle.  |
| 2. | 8 cases—left ventricular anterior papillary muscle.  |
| 3. | 4 cases—left ventricular papillary muscle, but whether anterior or posterior was not stated. |
| 4. | 2 cases—right ventricular papillary muscle.  |
| 5. | 1 case —left ventricular papillary muscles, anterior and posterior.                          |
- 

descending branch of the left circumflex artery. Rupture of the posterior papillary muscle of the left ventricle, on the other hand, has been found associated with obliteration of the right coronary artery or circumflex branch of the left coronary artery. However, not every case of spontaneous rupture of a papillary muscle has been found to be preceded by coronary occlusion.

Dévé (13) found no disease of the coronary arteries in the autopsy of his patient. Teacher (14) described extremely severe coronary arteriosclerosis, but no thrombi and no extensive myocardial infarction. However, patchy infarction of the papillary muscle was noted. Lipscomb's patient (3) also had neither coronary artery occlusion nor gross infarction; but there was some degree of coronary arteriosclerosis and petechial pericardial hemorrhages were present. There was no coronary occlusion or thrombosis in Askey's cases.

Analysis of the cases shows that the great majority of spontaneous papillary muscle rupture occurred secondary to coronary artery occlusion and associated myocardial infarction. However, in several instances (see Table I) a coronary artery thrombus was not demonstrated and arteriosclerosis of the coronary artery tree was minimal. In this connection the concept of coronary insufficiency is pertinent. The disproportion between myocardial nutritional demand and coronary blood flow, conceivably may be responsible not only for extensive papillary

muscle necrosis in the absence of striking coronary artery disease, but may also exaggerate the myocardial lesions even in the presence of a thrombotic coronary artery occlusion.

A number of studies in regard to coronary insufficiency have been presented within recent years (15-19). Briefly, the pathologic myocardial alterations are characteristic and consist mainly of focal or diffusely mottled or hemorrhagic areas of the subendocardial region of the left ventricle. The papillary muscles, particularly the posterior, show the predominant lesions. In more severe cases the lesions appear as confluent areas of myomalacia, involving almost any portion of the left ventricle, but again usually confined to the subendocardial zone. The characteristic location of the lesions, particularly in the posterior papillary muscle, was ascribed to the remoteness of these areas from the source of blood supply. It has been further emphasized that the subendocardial layer and papillary muscles are rich in capillary and precapillary anastomoses, and require an abundant blood supply and that anoxia is more readily manifested in these areas. Furthermore, the papillary muscles do comparatively more work than other portions of the myocardium and react more readily to oxygen lack. Acute coronary insufficiency may occur without concomitant coronary artery disease (20-22). The author has seen instances after acute hemorrhagic pancreatitis, and in severe aortic insufficiency, where the electrocardiogram showed definite evidence of acute coronary insufficiency, and coronary artery involvement was shown to be minimal.

The foregoing considerations suggest that coronary insufficiency may be the common denominator in instances of spontaneous papillary muscle rupture, with or without coronary artery occlusion. A meagre collateral blood supply to the superficial bulbospiral muscle which forms the left posterior papillary muscle, may be a contributing factor.

*Clinical features and differential diagnosis.* Lowry and Burn (5) stated of spontaneous rupture of a papillary muscle that "the condition is so rare and so lacking in distinctive clinical features, that it defies diagnosis except at the autopsy table". Probably the most important fact which denies the opportunity for the correct ante-mortem diagnosis of rupture, is the frequent almost immediate death of the patient following such rupture. The subjective symptoms are of no particular aid, since they are usually those of acute myocardial infarction. The presence of an accompanying murmur is of little aid. The majority of murmurs reported have been apical in position. Nineteen cases had abnormal heart sounds recorded (Table I). Of these, thirteen cases had a systolic murmur at the apex. Four of these were accompanied by apical diastolic murmurs. There was one instance of a systolic murmur at the base, and one of a diastolic alone, at the apex. In one case murmurs were present but were not described. In another "loud noises" were described over the precordium but were otherwise not specified. In the case of Lowry and Burn, what was originally thought to be a friction rub (and in retrospect a murmur) was heard in the fourth interspace just to the left of the sternum.

It appears, however, that the clinical diagnosis of a ruptured papillary muscle

may be considered in a patient with evidence of recent myocardial infarction and with a change in the character and intensity of a murmur which antedated the infarction. The murmur is usually mitral in position, systolic in time, and becomes loud and harsh. Or, in a patient known not to have had any cardiac murmurs, an acute myocardial infarction develops, and some time during the course of the illness a harsh mitral systolic murmur appears. There is usually a sudden radical change in the patient's condition associated with the occurrence of the muscle rupture. Indeed, as has been already stressed, rapid exitus is common. Nevertheless, keeping the above points in mind, and given a situation where sudden death does not occur, the diagnosis may be entertained.

Moragues (4) stated that his case was the second reported with acute pulmonary edema, on the basis of acute mitral insufficiency, and that the only other similar instance, that of Wankel (23), was also one of a left anterior papillary muscle tear. It should be made clear that in rupture of a left papillary muscle (as in case #1 herein reported) the same picture of acute mitral insufficiency can and does occur, and is a logical result of the rupture of either papillary muscle of the left ventricle.

The appearance of a murmur, or alteration in character of a long standing cardiac murmur possibly due to a papillary muscle rupture, requires differentiation from firstly, ruptured mitral chordae tendineae. In this connection although the murmur may be similar, the symptoms which appear after rupture are not specific, and the patient almost invariably lives on for a comparatively long period of months and even years (24). In a case of ruptured papillary muscle there is usually evidence of a cardiac catastrophe and death almost always occurs within a short period of time.

Rupture of an aortic cusp may offer differential difficulty. In such a case a murmur appears or an old one changes its character. However, it is best heard at the aortic rather than at the mitral area.

Finally, papillary muscle rupture is to be differentiated from acute perforation of an infarcted interventricular septum. Sager (25) pointed out that the murmur is best heard along the left sternal border at the fourth left interspace, and is similar in character to that due to the congenital type of septal defect.

#### SUMMARY AND CONCLUSIONS

1. The literature on spontaneously ruptured papillary muscle of the heart has been reviewed since 1935. To the 20 cases recorded at that time, 6 others found in the literature, 2 cases by courtesy of personal communications, and three personal cases have been added.

2. The first reported case of a clinical diagnosis of a ruptured papillary muscle has been presented herein.

3. The etiological mechanisms are discussed, including the possible relationship of the rupture of a papillary muscle to that of acute coronary insufficiency.

4. The clinical features and differential diagnosis have been reviewed.

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## REVERSIBLE BRONCHIECTASIS<sup>1</sup>

HERMAN HENNEL, M.D.

Reversible bronchiectasis is no longer an unfamiliar term (1-5). However, the reported cases are still relatively few, and the degree of bronchiectasis they show is relatively slight. The following case is of interest because (1) it demonstrates clearly that even what appears to be advanced bronchiectasis may prove reversible; (2) it illustrates the presence of reversible and irreversible bronchiectasis in the same lobe; and (3) it sheds light on the probable mechanism of bronchiectasis as well as the factors which favor reversibility.

*History.* (Adm. #553410) R. W., a white unmarried female, 30 years of age, was admitted to The Mount Sinai Hospital on August 27, 1946, complaining of increasing cough productive of large quantities of sputum, left lower chest pain and of recurring febrile episodes for nine months. Four years before admission the patient was treated for cavernous left lung tuberculosis which was discovered accidentally during a survey. She received pneumothorax therapy for two and a half years which promptly brought the tuberculous process under control. She made a satisfactory clinical recovery and remained entirely well until November, 1945, nine months before her present hospital admission. Her present illness began with an upper respiratory infection which was soon followed by increasing fever, cough productive of blood-tinged sputum, pain in the left chest and signs in the left lung which led to a diagnosis of virus pneumonia. The patient was hospitalized for one month in another institution. Her response to therapy with sulfa and penicillin was not satisfactory; and though she improved considerably during her month's hospital stay she did not completely recover. During the ensuing seven and a half months she continued to have cough productive of increasing amounts of sputum. The latter was frequently blood-tinged or frankly bloody, often foul smelling and the amounts varied from 4 to 6 ounces in 24 hours. The pain in the left chest varied from time to time and was rarely entirely absent on deep respiration. On several occasions she had moderate rises in temperature lasting one to several days. She felt ill most of the time and lost 15 pounds in weight during this period. Repeated search for tubercle bacilli in the sputum yielded negative results. The patient was regarded as a case of chronic bronchiectasis in the left lower lobe and was referred to The Mount Sinai Hospital for intensive penicillin therapy and/or lobectomy.

*Examination.* Physical examination, on admission, revealed a chronically ill female in fair nutrition and fair general condition. She had no fever. Her pulse rate was 80 per minute, her heart was normal and the blood pressure was 100 systolic and 60 diastolic. The right lung showed no abnormality. There was impaired resonance at the left base. A few fine and medium squeaks were heard throughout the left lung. Over the left lower lobe the breath and voice sounds had a bronchial quality, and moist as well as dry rales were elicited in this area. The left lower lobe appeared considerably decreased in size as judged by the marked displacement of the heart toward the left side. Postural drainage yielded about 1½ ounces of thick greenish purulent sputum, blood tinged, but without odor. The fingers showed early clubbing and there was floating of the nail beds.

*Laboratory data.* The sedimentation rate was 35 mm. in one hour. Hemoglobin was 75 per cent; white blood cell count was 7,400 with a normal differential; red blood cell count was 3,760,000. An electrocardiogram showed no abnormality. A sputum culture yielded

<sup>1</sup> From the Second Medical Service and the Group for Thoracic Diseases, The Mount Sinai Hospital, New York.

Presented at the Thoracic Diseases Conference, February 3, 1947, at The Mount Sinai Hospital.

a pure growth of *Staph aureus*. Numerous sputa were negative for tubercle bacilli. Gastric washings were negative for tubercle bacilli on smear and later on culture. Urinalysis was negative. X-ray examination on admission (fig. 1) showed a minimal tuberculous process in the extreme apex of each lung, but no evidence of recent infiltration. The left lower lobe was dense and much shrunken in size, as shown by marked displacement of the heart to the left. Bronchographic examination on September 9, 1946 (fig. 2a and b) disclosed the presence of marked cylindrical and saccular dilatation of all the branches of the left lower lobe. Bronchoscopy shortly after admission showed the bronchi of the right lung to be normal. There was no evidence of obstruction, stenosis or ulceration in the bronchi of the left lung. The left lower lobe bronchus was displaced downward. There was a profuse amount of non-foul purulent secretion from all the divisions of the left lower lobe bronchus. The pus rapidly reappeared after suction from the apical and lower paravertebral divisions of the left lower lobe. No pus was seen coming from the left upper lobe bronchus.

*Course.* There was a low grade fever on several occasions during the first two weeks. On September 1, penicillin therapy was started. During the first week it was given by

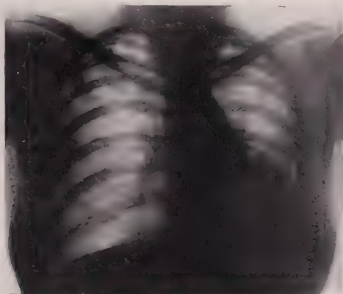


FIG. 1. Roentgenogram made on August 28, 1946, on admission, showing minimal tuberculous process in the extreme apex of each lung but no evidence of recent infiltration. The left lower lobe is dense and shrunken in size. The heart is displaced to the left.

aerosol only, 100,000 units in 1 cc. of normal saline every 4 hours, 5 times a day. Postural drainage was practiced before each treatment. On this regimen moderate improvement in cough and expectoration was noted. On September 9, the patient began to receive, in addition to aerosol penicillin, 500,000 units of penicillin in emulgen by intramuscular injection once a day. On September 12, the sputum was recorded as markedly decreased in amount. On September 22, it was recorded that the patient had no sputum even on postural drainage during the preceding 36 hours, with less than 5 cc. in 24 hours for two days prior to that time. Penicillin therapy by both routes was continued until September 29 (a total period of three weeks), and aerosol therapy alone was maintained for the remainder of a six weeks period. The patient was discharged from the hospital on October 16, in excellent general condition with no cough and with less than 2 cc. of purulent sputum every 1-2 days obtained only on postural drainage after induced forceful coughing.

This clinical improvement was matched by the marked resolution of the disease process in the left lower lobe as disclosed by x-ray examination. On October 11, (fig. 3a) the film showed marked resolution of the inflammatory process in the left lower lobe since the examination on August 28, 1946. On January 10, 1947, bronchographic examination was repeated. The bronchogram (fig. 4a,b,c) showed persistence of the bronchiectasis in the

apical branch of the left lower lobe. However, the lower paravertebral and lateral divisions of the left lower lobe bronchus showed an almost normal appearance in all the views, demonstrating reversal of the bronchiectasis process in the area.

The patient has since been observed repeatedly in the follow-up clinic. When last seen on April 21, 1947, her cough and expectoration had remained minimal, her general condition was excellent and she was able to return to her normal occupation. X-ray examination of the lungs at that time showed no recurrence of the infiltration in the left lower lobe (fig. 3b).

*Discussion.* Whether this satisfactory clinical state will be maintained indefinitely cannot be predicted. It should be recalled that the patient still has extensive bronchiectasis in the apical division of the left lower lobe in which infection may recur and from which spillover infection to the other bronchi may take place. It may even be necessary to resort to lobectomy before a cure can be achieved in this case. It is of interest, nevertheless, that with penicillin therapy it was possible to clear up the infection in all the bronchi, and to bring

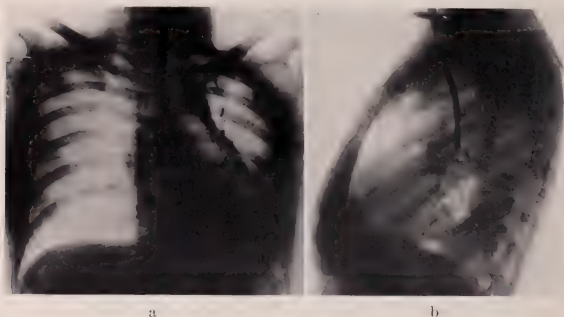


FIG. 2a, b. Bronchogram made on September 9, 1946 before treatment was instituted, showing marked cylindrical and saccular dilatation of all the branches of the left lower lobe.

about resolution of the atelectatic pneumonia in the lower part of the lower lobe. But the notable feature of the case is, that with the clearing of the atelectatic pneumonic process in the lower portion of the left lower lobe, there was a reversal of the bronchiectasis in this area. This demonstrates the possibility of reversibility of early bronchiectasis even when of as marked degree and extent as in this case.

It is to be noted that at the same time that the bronchiectasis in the apical region remained unchanged even when the infection within the dilated bronchi had been controlled with penicillin therapy. Obviously, in the latter portion of the left lower lobe, the bronchial and parenchymal injury was severe, leading to permanent organic changes; while in the lower portion of the left lower lobe the bronchial changes were largely functional in nature, and reversal was therefore feasible.

This brings up the question of the pathogenesis of the type of bronchiectasis that may be reversible. In a report of a group of cases (6) illustrating how

rapidly bronchiectasis can develop in the course of atelectatic suppurative bronchopneumonia, I stressed the importance of the factor of increased and direct pull on the bronchi in an atelectatic lobe, a condition which favors their dilatation. Normally the pull of the expanding thorax during inspiration is transmitted to the bronchi very feebly because of the intervening functioning elastic lung. When atelectasis develops, the intrapleural pressure becomes

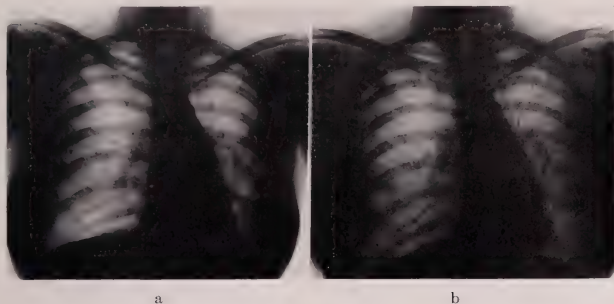


FIG. 3a, b. Roentgenogram made October 11, 1946 and April 21, 1947 showing marked resolution of the atelectatic pneumonic process in the lower half of the left lower lobe.

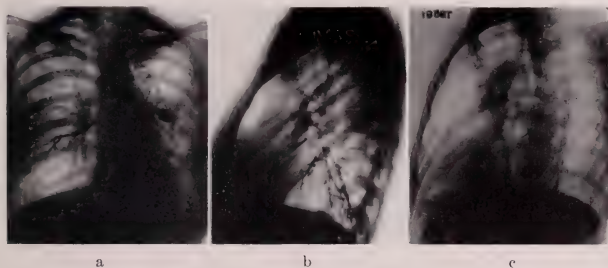


FIG. 4a, b, c. Bronchograms made on January 10, 1947 showing reversal of the bronchiectasis in the lower paravertebral and lateral branches of the left lower lobe. There is persistence of the marked bronchiectasis in the apical division of the lobe.

much more negative and the pull on the lung may be many times the normal; and this pull is exerted directly on the injured bronchi in the solid atelectatic lung. Bronchiectasis may, and probably often does, result under these circumstances. According to Doctor Harry Wessler, paersis or the bronchial musculature, toxic or nervous in origin, may be a major factor favoring bronchial dilatation in the presence of atelectatic pneumonia. If this condition is not permitted to continue, and the function of the atelectatic lung is restored, the bronchiec-



tasis may prove reversible. Once organic injury of the bronchial wall has taken place only repair (by fibrosis) is feasible and permanent bronchiectasis may result.

In the case under discussion the atelectatic bronchopneumonia was apparently beneficially influenced by penicillin therapy. In other reported cases spontaneous cure occurred, namely resolution of the atelectatic pneumonia and reversal of early bronchiectasis. The value of pneumothorax therapy in the management of early bronchiectasis developing in the course of atelectatic suppurative bronchopneumonia was discussed in an earlier publication (6). It was then suggested that chemotherapy might become an effective weapon for the control of bronchiectasis in its early phase, when still reversible, before permanent organic changes in the dilated bronchi has taken place. The experience in this case appears to justify that prediction.

The case is of interest because it illustrates the coexistence of the two types of bronchiectasis—reversible and irreversible—in the same lobe and the difference in their response to medical management.

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## THE TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH NAPHRIDE SODIUM<sup>1</sup>

REUBEN YONTEF, M.D.

Many forms of treatment, especially the use of the heavy metals, have been advocated for the treatment of chronic discoid lupus erythematosus. The gold salts and bismuth are probably the most often employed. However, gold therapy has its drawbacks in that the use of the gold salts is not infrequently accompanied by toxic reactions. In a number of instances, exfoliative dermatitis has developed. Such sequelae have occurred frequently enough to deter many physicians from using gold therapy. In addition, many of the patients after initial improvement following the use of the gold salts, become resistant to subsequent administrations.

Bismuth has become popular in the treatment of discoid lupus erythematosus not because it is more effective than the gold salts, but because toxic reactions following its use are seldom seen.

In 1938, naphuride by its old name of *germanin* was advocated as a substitute for gold therapy in the chronic form of lupus erythematosus by Peck at the Mount Sinai Hospital. Naphuride sodium is the sodium salt of symmetric bis (meta-amino-benzoyl-meta-amino-paramethylbenzoyl-1-naphthylamino-4:6:8:trisulfonic-acid) carbamide. Naphuride, which is similar to Bayer 205, was originally used as a trypanosomicide for the prophylaxis and treatment of African sleeping sickness. Later, it was also advocated for the treatment of pemphigus.

Many dermatologists are convinced that naphuride is too toxic to be used in most conditions. This is based on the relatively large doses employed in the treatment of pemphigus. For the treatment of chronic discoid lupus erythematosus, Peck has advocated that the dosage be kept low. According to his directions, the initial dose 50 mgm. with a gradual increase to a maximum of 200 mgm. given once a week. Rarely, is it necessary to exceed this dosage. A total of twelve weekly injections are given and in the usual patient, the total amount should not exceed  $2\frac{1}{2}$  grams. This course of naphuride is followed by a rest period for about three months. If there are still evidences of activity during this three month period, a course of bismuth or crude liver injections may be given. The naphuride may then be repeated for another twelve injections if necessary.

Just as with other drugs of the heavy metal group, naphuride sodium may have a toxic effect on the kidney. In order to lessen this possibility, the patient should have a weekly urine examination prior to each injection. This drug is contraindicated in patients with albumin or casts in the urine. In large doses, naphu-

<sup>1</sup> From the Service of Dr. Samuel M. Peck, Department of Dermatology, The Mount Sinai Hospital, New York.

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ride may have a hemolytic action. Sensitivity reactions sometimes occur with this drug. They are characterized by erythematous, itching, maculo-papular eruptions. Other toxic effects reported are chills, fever, headache, nausea, stomatitis, cutaneous hemorrhages, hemoglobinuria and even agranulocytosis. Naphuride sodium is slowly eliminated and has a cumulative action.

#### CASE REPORT

*History.* (Clinic Chart #33-1348) B. B., a white woman, aged 40 years, was first seen in the dermatology Clinic in 1926. At that time, she gave a history of an eruption on the face which had been present for approximately one year. The eruption of sudden onset apparently appeared after exposure to strong sunlight. A diagnosis of chronic discoid lupus erythematosus was made. At that time, gold sodium thiosulfate was given alternating with courses of bismuth. By 1930, the patient was practically well except for one small lesion on the left cheek. In 1932, following another exposure to the sun there was a recurrence. She was again treated with gold sodium thiosulfate. During 1933 and 1934, she suffered a number of flare-ups with lesions appearing on the forehead. The treatment at that time consisted of light protective creams, gold and bismuth. During 1934, many other methods of treatment were tried with disappointing results. In November, mucous membrane lesions were noted for the first time. In 1935, she was treated in the hematologic Clinic by Dr. Peck with a series of local injections of Athrox Bothrop's venom in an attempt to obliterate the telangiectatic lesions. She received 12 injections of from 0.1-0.2 cc. of a 1 to 1000 dilution given intradermally. There was some obliteration of the telangiectatic lesions and, strangely enough, marked regressions of the other lesions. She was not seen again for three years. In 1938, she returned to the clinic with the history of a recurrence in 1937. Examination revealed typical lesions over both eyebrows and cheeks with the former sites, especially on the cheeks, showing a marked subcutaneous infiltration. She was again treated with gold and bismuth with disappointing results. In 1939, naphuride sodium under the old name of *germanin* was used for the first time. It was given intravenously once a week in doses from 100 to 600 mgm. A total of 16 injections were given with spectacular results. In March 1940, there was a moderate recurrence of the lesions and she was again cautiously retreated with germanin for two months by the intravenous route with favorable results. Another recurrence was noted in September 1940 and in view of the fact that germanin could not be obtained, Athrox Bothrop's venom was again tried. At the sites where it had been given five years previously, no new lesions had appeared. A severe local reaction occurred after the first injection, severe enough to warrant stopping the drug. During the years 1941 through 1944, lesions gradually recurred on the face, new lesions appeared in the scalp and there was involvement of the buccal mucosa. Gold, bismuth, large doses of vitamin C and bismarsen were tried with very little benefit. When she returned for observation in the latter part of 1944, there were many typical lesions on the cheeks, forehead, eyebrows, upper two-thirds of the nose, scalp and mucosa of the mouth. There were also a number of subcutaneous infiltrations situated below the lesions on the cheeks. She was given a course of liver and vitamin C all without effect. From October 1945 to January 1946, she received 11 intramuscular injections of naphuride sodium; the initial dose was 100 mgm. with a gradual increase until a maximum of 300 mgm. was given. The injections were given weekly. A rapid improvement was noted and the subcutaneous infiltration began to involute. Following these 11 injections, she was given a course of bismuth and crude liver intramuscularly as interim therapy. On April 1946, slight activity was again noted and another course of 8 injections of naphuride was given. She was then given a three month rest period and again naphuride was given for 7 injections. At the last injection, the patient complained of severe nausea, dizziness, sluggishness and generalized malaise, and treatment was stopped. At the present time, while most of the lesions had regressed, there are still a number of active lesions to be seen on the face. In addition, there is a marked loss of subcutaneous fat with scarring over the flush areas of the cheeks.

*Laboratory data.* Frequent urine analyses were performed before each injection of naphuride. At no time was there more than a slight trace of albumin. Occasionally a few red and white cells were also found, but the specimens were not catheterized. Numerous blood counts were normal.

*Comment.* A biopsy was not performed in this case. From the typical appearance, there is no question that we are dealing with a chronic discoid lupus erythematosus. However, the large infiltrated subcutaneous lesions are considered to be of the type described by Bechet and by Irgang. The former designated such lesions as *lupus erythematosus hypertrophicus et profundus* and the latter as *lupus erythematosus profundus*.

Because of the marked cosmetic defects due to the disappearance of the infiltrative part of the lesions and the destruction of the subcutaneous fat, an attempt at cosmetic repair was made by Dr. Michael L. Lewin. Dr. Lewin found that there was an atrophy of the Bichet's fat pad in the cheeks, more pronounced on the right than on the left. The skin on the face was also heavily wrinkled as a result of the loss of the panniculus. At the time of Dr. Lewin's examination, the only active lupus erythematosus lesions were small patches on the left cheek, left intraorbital region and on the dorsum of the nose with some superficial scarring in these areas. Dermal grafts were used to correct the depression on the patient's face. Only the dermal component of the graft was utilized so that future shrinkage should be limited to about 50 per cent.

There was a very satisfactory cosmetic result. On the left side, because of the poor vitality of the skin and the presence of remnants of the infiltrations previously described, a smaller graft was inserted than would have been desirable.

#### SUMMARY

A case of chronic discoid lupus erythematosus is presented with tumidous lesions suggestive of Boeck's sarcoid, who had been treated for 20 years with over 150 injections of gold sodium thiosulfate, over 50 bismuth injections plus practically all known forms of therapy for this condition. The best results were obtained with naphuride sodium. A cosmetic repair of the resultant scarring and atrophy is described.

There have been many cases of lupus erythematosus treated in the dermatology Clinic with naphuride sodium. The results with this drug compare very favorably with either gold or bismuth. This was especially noticeable in those cases where there had been poor response to the use of bismuth or gold before the naphuride was used. Naphuride sodium is not a dangerous drug provided that it is given with caution and careful urine examinations are made before each injection.

# VENOUS THROMBOSIS AND PERIPHERAL PULMONARY EMBOLIZATION\*

## PART I

HAROLD NEUHOF, M.D.

### CHAPTER 2

#### ATYPICAL FORMS OF VENOUS THROMBOSIS

The fact that venous thrombosis in the lower extremities pursues a silent course in perhaps a quarter of all cases has been alluded to in the foregoing chapter. Reference also was made to the usual local and constitutional manifestations of venous thrombosis. Furthermore, emphasis was placed on the possibility of an exclusion diagnosis of venous thrombosis, in cases of more or less prolonged tachycardia and low grade fever, even in the absence of local signs of venous thrombosis. A study of the verified cases of venous thrombosis which have been under our observation reveals many that were atypical. It is important to become acquainted with the atypical forms, for they are not uncommonly encountered and should be recognized promptly in order to institute appropriate treatment. Indeed, prompt action may be required in some of these cases in order to prevent death, action which is not possible, of course, without such recognition.

Some of the variations to be described have unquestionably been observed by others but do not appear to have been set forth in the literature. In any event, they are gathered together and presented; similar observations by others will have to await further literature on the subject.

A. *Prolonged fever in venous thrombosis.* Fever of low grade or at higher levels for several weeks is common enough in uncomplicated venous thrombosis to be regarded as in keeping with the condition. Elevated temperatures for longer periods, particularly when associated with tenderness and thickening along the course of the femoral vein, is generally regarded as indubitable evidence of the existence of thrombophlebitis. This would be a matter for only theoretical consideration were it not for the fact that whereas conservative treatment is usually regarded as indicated for thrombophlebitis, active therapy should be decided upon in the presence of venous thrombosis. Therefore, the fact that prolonged, irregularly elevated temperatures may occur in venous thrombosis of one or of both lower extremities is of clinical importance. This picture was seen in several cases in which more or less obvious signs of venous thrombosis existed. Illustrative instances will be briefly cited:

A woman aged 45 years, after having been discharged following an appendectomy, returned to the hospital two weeks later with fever and local signs of venous thrombosis in

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\* This is the second of a series of chapters dealing with this subject which comprises part I of the forthcoming monograph on Venous Thrombosis and Pulmonary Embolism. Part II has already appeared in earlier numbers of this Journal.



both lower extremities. Fever pursued a high and irregular course for four weeks. At the end of this time the diagnosis of pyelphlebitis was entertained, as the manifestations in the legs had partly subsided. Exploration of the femoral veins was decided upon, however, with the thought that exploration of the portal vein might be in order if the exploration of the femoral veins was negative. On each side a partly organized thrombus in the femoral vein was encountered. In both the clot extended into the external iliac vein where it was capped by a soft, red thrombus. Fever subsided after extraction of the thrombi and ligation of the femoral veins.

There is a similar, but much more protracted and outspoken, case in the older Mount Sinai Hospital records which was not operated upon and came to autopsy. Now by way of contrast a second case is cited:

A woman, aged 53 years, had had a prolonged episode of venous thrombosis in both lower extremities in 1932. There remained some left-sided swelling which waxed and waned. For many months before this patient came under observation there was fever which was more or less continuous, some elevation of the temperature always being recorded when she felt feverish and took her temperature. At times the fever reached 101°F. There was occasional pain in the left calf. An episode of vertigo led to a general examination, which was negative. Examination of the left leg revealed tenderness and infiltration in the left calf. Fever subsided after ligation of the left common femoral vein.

The reason for prolonged fever in the presence of bland venous thrombosis is not clear. One may postulate a reaction to a protein derived from the thrombus and swept into circulation, or discharge of small thrombi into the venous system at frequent intervals. The prompt cessation of fever after operation appears to establish that the lesion was in the nature of venous thrombosis and not of pulmonary embolization, but does not exclude the possibility that fever in these cases may be due to a low-grade infection of the thrombus or of the wall of the vein bearing the thrombus.

*B. Chills and fever in venous thrombosis.* The foregoing section contains the group of cases in which fever, a common enough concomitant of venous thrombosis, pursued an unusually prolonged course or was at unusually high levels. Reference is made here to chills and fever during the course of bland venous thrombosis, as noted in a number of cases. Sepsis derived from suppurative phlebitis is a well known state often referred to in the literature, in contrast to chills and fever complicating bland venous thrombosis, to which reference in the literature is not found. It may be stated at once that the evidence establishing the blandness of the thrombus is for the most part indirect. The possibility exists, at least in some of the cases, that the thrombus may have been infected at the source, but was capped by a bland thrombus. Nevertheless, a study of the cases indicates the extreme unlikeliness of the existence of infective foci from which an inflammatory lesion of a vein could have been derived. The prompt subsidence of chills and fever after simple surgical treatment (ligation of the femoral vein) also militates against such an assumption. Finally the absence of infection is established at autopsy in a fatal case to be reported. It may be assumed, until proven otherwise, that the chills and fever may be similar to protein reactions seen after injections of milk, for example, and not due to infection.

In most of the cases pulmonary embolization was known to exist and may also have been present in a silent form in the remainder of the cases. There is, therefore, the possibility that the chills and fever are referable to the foci in the lungs rather than to the bland thrombosis in the lower extremities. Whatever the mechanism which leads to chills and fever in unusual cases of bland venous thrombosis, the important point is to recognize such cases for what they are and not to assume that they are of septic nature. It is the difference between the administration of antibiotic medication, which will not prevent the development of pulmonary embolism, and the prompt institution of measures to prevent such embolization. Delay in operation was the cause of the fatality in the first case, in which the bland nature of the thrombi was established at autopsy. The case can be reported briefly as follows.

A male, aged 32 years (Mount Sinai Hospital No. 492127), was admitted a month after a blunt injury to the left calf. There had been pain in the calf which had extended into the thigh. An episode apparently indicative of major pulmonary embolization occurred 6 days before admission and was followed by two others. Under hospital observation there were chills and fever, negative blood cultures, and the development of tenderness along the left femoral vein. Operation was decided upon only when the patient's general condition had greatly deteriorated. At operation the femoral and external iliac veins were found to be occupied by old thrombi; these were removed. The iliac vein was ligated when free bleeding was obtained. Death occurred shortly after operation. At the autopsy there were found a large free embolus in the right ventricle, multiple peripheral pulmonary emboli with and without infarction, and thrombi in the inferior vena cava and left common iliac vein. There was no evidence of infection in any of the thrombi.

The following case occurred during the course of pregnancy which, however, did not appear to play any significant rôle.

A month before admission, the patient, 25 years of age, apparently injured her left leg in a fall sustained in the fifth month of pregnancy. Two weeks later there was swelling of the left leg, fatigue, and an episode of dizziness and faintness. This was followed by fever (102° to 103°F.) and almost daily chills. Chemotherapy in full doses was without effect. A characteristic episode of pulmonary embolization (with positive roentgenogram) occurred. There was infiltration of the left calf and tenderness in the lower left thigh. The patient was operated upon on admission, two weeks after the onset of chills and fever. The femoral vein was transected; there was no thrombus at this level. Chills and fever did not return after operation, and infiltration in the calf soon subsided. There was no appreciable swelling of the leg when the patient was examined three months after normal childbirth.

In several cases there were only one or two chills, of which the following is an example.

A 32 year old woman (Mount Sinai Hospital No. 519704) had a Caesarean section 17 days before admission. On the fifth post-operative day there was a chill and rise of temperature to 105°F. Several days later there was evidence of venous thrombosis in the right calf, followed by an episode of pulmonary embolization. On admission, an operation was performed consisting of transection of the right femoral vein, at which level there was no thrombus. Subsequently fever without chills led to readmission for thrombosis in the left leg, for which ligation of the left femoral vein was performed.

The origin of the chills and fever was not certain in the following case, although the most likely source appeared to be the extensive area of thrombosis in the femoroiliac vein.

A woman, aged 39 years (Mount Sinai Hospital, P. P.), was cystoscoped and ureteral catheterization instituted. Several days later there was fever and an episode of severe pulmonary embolization. This was followed by a chill, fever, and the evidence of venous thrombosis in the right leg, extending upwards into the femoral region. At operation pronounced periphlebitis of the femoral vein was noted. There was a partly organized thrombus in the femoral vein, extending into the iliac vein. The upper end, which was free, presented a sheared-off surface, indicating a broken-off thrombus. The proximal fragment was not recovered despite suction catheterization; it was realized that it might have been left behind, even though free bleeding from the severed femoral vein was obtained. There were two chills, with fever to 104.6°F., in the first post-operative days, with gradual subsidence of fever thereafter. The post-operative chills and fever might have been due to a hematoma in the wound following the administration of heparin, but an additional thrombus in the iliac vein or in the pulmonary artery appears to be a more likely source.

The pulmonary lesion appears to have been the source of the chill and fever in the following case:

An unusually vigorous and active woman, 80 years of age (Mount Sinai Hospital, P. P.), and previously in good health, experienced a violent chill of 10 to 15 minutes' duration, followed by fever of 103.6°F., left thoracic pain, and unproductive cough. There were physical signs of consolidation in the left lower lobe. The onset was at 10 a.m. Five hours later the patient complained for the first time of pain in the left leg. By that evening the left leg presented objective evidence of a venous thrombosis. Heparin therapy was employed, followed by dicoumarol. The fever subsided after several days, and the other signs of venous thrombosis soon disappeared.

*C. Pulmonary embolism, the dominant feature.* The last case in the preceding section represents an intermediate condition between cases in which the symptoms and signs of pulmonary embolism antedate those of venous thrombosis, and an important group in which symptoms and signs of venous thrombosis either do not appear at all or become evident very late. Reference is not made here to the lethal type (presented extensively in Part II), in which death occurs suddenly and without warning.

In all the cases of this group the manifestations of pulmonary embolism dominate the clinical picture. In some there is only a single episode; other patients have repeated attacks, which may recur for several weeks or months before there is any evidence of venous thrombosis in the lower extremities. A remarkable feature of many of these cases is the paucity of signs of venous thrombosis when they do appear. The following case is typical.

A woman, aged 32 years, with a well compensated mitral stenosis, but otherwise in good health, suffered a severe attack of pulmonary embolism, with thoracic pain, cough and hemoptysis, which was at first believed to originate in the heart. Three additional episodes in the next two weeks led to an examination of the legs as the probable source. Infiltration of the left calf, with questionable tenderness, was noted. Inquiry then led to the history of an insignificant injury to the left calf two weeks before the first episode of pulmonary embolism. There was no additional embolization after ligation of the left femoral vein.

The following fatal case is described because of the somewhat obscure clinical picture and the findings at autopsy. The case can also serve as an example of the next section which deals with venous thrombosis in ambulant patients. Only the salient features will be mentioned.

A woman, 46 years of age (Mount Sinai Hospital No. 446071), had had several episodes of "pleurisy," the first at the age of 28. Four days before admission, while dancing, the patient fainted and was said to have been unconscious for an hour. Some frothy material was expectorated. Subsequently there were pain in the right chest and dyspnea. Temperature on admission was 103°F. which soon dropped to normal. An urticaria confused the clinical picture. The electrocardiogram was consistent with myocardial involvement. Subsequently, progressive enlargement of the heart was noted. At a later stage there appeared evidence of venous thrombosis in the right leg. Death occurred four weeks after admission to the hospital. Thirty-six hours before death, when the patient appeared to be in fairly good clinical condition, she suddenly became very agitated and apprehensive, but suffered no pain. There was pronounced asthenia, pulse was barely perceptible, blood pressure dropped sharply, and respirations were rapid. Some improvement occurred with oxygen and morphine therapy. A second episode was fatal. Autopsy showed an organizing embolus in the left main pulmonary artery and a recent embolus in the right main pulmonary artery. There were large thrombi in the right auricle, some of which were loosely attached, and one in the inferior vena cava. There were recent pulmonary emboli. An old "infarct" scar in the left lower lobe suggested the previous occurrence of an episode of pulmonary embolization. The veins of the legs could not be examined.

D. *Ambulant patients with venous thrombosis.* The scanty reference in the literature to this group may be due to its comparative rarity. Its importance, however, is out of all proportion to its relative infrequency. These cases are atypical, but their recognition need not be delayed for that reason. Too much emphasis cannot be placed on the fact that adults who are well, have not been in bed for days or longer because of a surgical or medical illness, and have had no injury to the legs, may none the less develop venous thrombosis. The clinical importance lies in the related fact that the first sign may be the appearance of pulmonary embolism. Indeed, one may assume that not a few of the cardiac deaths ascribed to lesions of the coronary vessels are due to pulmonary embolism. At any rate, massive pulmonary embolism at times is found at autopsy to be the cause of death in cases in which coronary occlusion was the assumed cause.

There are reports in the literature dealing with obscure sources of pulmonary embolism aimed to establish that there are other sources than the lower extremities for such emboli. An analysis of reported cases reveals that in the great preponderance a post-mortem examination has not been made. Similarly, papers ascribing sudden death to coronary occlusion (in elderly officers in the past war, for example) are incomplete in the absence of post-mortem examination. The tragedy of sudden death or sublethal states due to coronary occlusion is, of course, conceded. Simulation by pulmonary embolism, however, must also be recognized, a simulation which may be so close that clinical differentiation is impossible even to the expert. This is dealt with fully in Part II, but is emphasized here because the form of venous thrombosis as seen in ambulant individuals may be complicated unexpectedly by pulmonary embolization.



The emphasis in this section has been placed on the complicating feature of pulmonary embolus, which has characterized all the cases of venous thrombosis which I have seen in ambulant individuals. However, varying grades of venous thrombosis confined to the calf veins and uncomplicated by pulmonary embolism are not uncommon and do not reach the hospital because of the absence of complications. The following are illustrations of cases from personal experience.

A middle aged man who apparently had not been ill was standing before a mirror shaving when he collapsed suddenly and without warning. Subsequent observations established this as an episode of severe pulmonary embolization, which was followed by another; later, the presence of venous thrombosis in the right leg gradually became obvious. The cause was possibly an old phlebitis at the ankle. The patient was operated upon and an extensive thrombosis in the femoral and iliac veins was encountered. (These features are referred to in the section dealing with the treatment of femoroiliac thrombosis.)

In the foregoing case the symptoms and signs of venous thrombosis followed those of pulmonary embolization and were insignificant at their onset. In contrast, the following is a remarkable case.

A man had had a venous thrombosis in the right leg 2 years before. At that time there was no etiology and he had not been in bed for any illness. He had had pain in, and progressive swelling of, the calf for three weeks and there was clear objective evidence of venous thrombosis. Operative treatment was instituted. The femoral vein was divided and the procedure was followed by subsidence of manifestations of thrombosis. Six weeks before the present hospital admission a bilateral orchietomy for cancer of the prostate was performed. The patient was confined to bed only one day and soon returned to his occupation. Four weeks later there were the first symptoms of venous thrombosis in the left leg. When seen at the office one week later (one week before hospital admission) he showed obvious evidence of a venous thrombosis apparently confined to the calf. Treatment was deferred in the hope of spontaneous recession in a patient with an otherwise hopeless disease. Upon the report of a transient "weak spell" one week later the patient was promptly hospitalized and operated upon. A femoroiliac thrombosis was encountered, the details of which are reported in the section dealing with the surgical treatment of that condition. The thrombus was removed and the vein ligated. The further course was uneventful.

A heavily-built physician, aged 58 years, had had pains in his calves, chiefly on walking, for several years. Examinations had excluded arterial disease in the lower extremities but had not established the existence of venous thrombosis. He died suddenly while driving his car. The autopsy revealed a massive pulmonary embolus as the cause of death. In the absence of other findings this was assumed to have been derived from the leg.

There may be some question as to the relationship of the venous thrombosis to operation in the following ambulant patient because the time interval between operation and the onset of clinical manifestations was so long. If related to operation the case also illustrates the occasional impossibility of establishing clinically a diagnosis of venous thrombosis. The tragedy inherent in delay in therapy, even in a case in which the diagnosis is doubtful, is also to be seen.

A woman, 40 years of age, was subjected to cholecystectomy for chronic cholecystitis and cholelithiasis. The case was selected for operation by an applicant for fellowship in the College of Surgeons and was most carefully followed after operation. The post-operative course was entirely uneventful and it is to be especially noted that daily examination of the legs was made, which was consistently negative for thrombosis. The patient left the



hospital on the eleventh day after operation. Two and a half weeks later there was an episode of transient syncope with subsequent complaint of asthenia. When seen at the office three days later the patient had fully recovered and examination was negative except for trivial findings in the legs (in which, in fact, another observer did not concur) as follows: Infiltration in the right calf without tenderness, questionable infiltration but tenderness in the left calf. The patient was sent home because hospitalization was not obtainable. The next day there was an episode of sudden collapse followed by death in one-half hour. The physician who was called was not satisfied that the death was cardiac and an autopsy was performed. This revealed an occluding main stem pulmonary embolus.

The following instance of venous thrombosis in an ambulant individual illustrated also the possible dangers of anticoagulant therapy.

A young woman had an entirely uneventful convalescence after normal childbirth followed by early ambulation. Four weeks later, while in another city, symptoms of venous thrombosis in the left leg appeared. She returned to New York and was placed on heparin followed by dicoumarol therapy. There was partial subsidence of signs and symptoms of venous thrombosis. On the fourth day an episode of mild pulmonary embolization occurred, anticoagulant therapy was discontinued and operation consisting of severance of the femoral vein was performed. The subsequent course was uneventful.

*E. Atypical pathology and related symptomatology.* Between the extremes of venous thrombosis and thrombophlebitis various lesions have been encountered at operation, as would be anticipated. Variations in the forms and distribution of bland thrombi have also been met. Because of their clinical significance these atypical varieties with which the pathologist is undoubtedly well acquainted should be better known to clinicians than appears to be the case at the present time. Since with very few exceptions (Bauer, for example) there appears to be no significant literature on the varieties of venous thrombosis, reference cannot be made to the observations of others, although one may assume that atypical forms in addition to those now to be described have been noted. The main purpose here is to describe the unusual varieties which have been found to exhibit potential or actual clinical manifestations.

*Free thrombus in the iliac vein.* This is perhaps the most important variant of venous thrombosis in the lower extremities since it is certainly the most life threatening. This atypical form is not described in the literature and no statement can be made concerning its incidence except in my own experience. It has been encountered 8 times at operation under circumstances which will be related. All cases presented thrombosis in the femoral vein extending to or almost to the level of the inguinal ligament. Free thrombi in both iliac veins were present in one extraordinary case to be detailed. By way of contrast with the lack of clinical report of free iliac thrombi may be mentioned its not infrequent incidence at autopsy in cases of venous thrombosis of the femoral veins.

In my experience free iliac thrombi have been of the "killer" variety, single, of large diameter about that of the femoral vein, and up to three or more inches in length. Their lower ends were from an inch to two or more inches above the inguinal ligament. Because of facets at their lower ends one may assume that they had been detached from thrombi in the femoral vein. The reason they

remained, perhaps for long periods, in the iliac vein and did not ascend into the vena cava, is not clear. It may be that their upper ends lay athwart the entrance into the vena cava or that they remained in a form of venous *cul-de-sac* which is, in fact, the anatomical conformation at the confluence of external, internal, and common iliac veins. Whatever the mechanism, there is no justification for the belief that they are formed in the external or common iliac veins, a theory which formerly was stoutly maintained. They are identical with thrombi lodged in the pulmonary artery, and of the same source. Those conversant with Bauer's venographic demonstration of thrombi many inches long attached below and waving free above in the femoral or iliac veins will appreciate fully the source of these free iliac thrombi and will also assume that they must be far from rare.

The last mentioned assumption is the one to be particularly emphasized. The fact that a free iliac thrombus was encountered only a few times in one surgeon's experience has but little significance in a consideration of incidence. Of far greater significance is the fact that free iliac thrombi were found so often when it was learned that they were to be specifically sought for under circumstances now to be set forth. The essential point is that there are no symptoms and no signs to point to the presence of a free iliac thrombus. A discussion of the technique of operation will be taken up in its appropriate place. Here I would only mention that the technique employed for the exploration of the external iliac vein—transverse severance of the common femoral vein—offers a more liberal exploration of the interior than that which is generally advocated. This is mentioned in order to emphasize that bleeding which can be termed "moderate" to "free" took place from the upper cut end of the femoral vein in all the certified cases of free iliac thrombus. Indeed, there was scarcely any greater bleeding in these cases after the thrombus was removed. As stated, a discussion of different operative technics will be offered in a later section but it is apparent that the recognition and removal of a free iliac thrombus would be difficult, if not virtually impossible, through one of the slit incisions in the superficial femoral vein (or the common femoral vein, for that matter) which appear to be so commonly practiced at the present time for the removal by suction of femoroiliac thrombi.

The *first case* in which the iliac vein was studied specifically for the presence of a free thrombus was encountered about three years ago.

The patient had experienced one or possibly two episodes interpreted as massive pulmonary embolization about 2 weeks before, followed by fever. At operation a thrombus of the femoral vein, terminating a short distance below the inguinal ligament, was encountered. It was thought that an additional thrombus might be found in the iliac vein if sought for. A long, thick, free thrombus was found in the iliac vein. The interior of the iliac vein was explored in all subsequent cases in which patients had had obvious or suggestive episodes of major pulmonary embolization and in whom at operation the thrombus in the femoral vein terminated at or below the inguinal ligament.

It may be suggested here that some of the reported fatal as well as non-fatal cases of pulmonary embolism following ligation of the femoral vein, in cases of thrombosis of that vein short of the iliac, may have been due to the escape of an unrecognized free iliac thrombus. In an analysis of operative treatment which

will be made in a following chapter, some criticism will be made of techniques which appear to invite thrombosis above a ligature on the femoral vein. However, there is certainly no justification for the assumption that with good technique a large thrombus may or will at times form at and above a ligature on a femoral vein (or any other vein). Nevertheless, authors reporting major (fatal or non-fatal) pulmonary embolization following femoral vein ligation usually suggest or indicate that the thrombus came either from the opposite leg when only one vein was ligated (thus the argument for bilateral ligation) or was formed above a ligature and was derived from this source. In view of the experiences now to be related it is fair to assume that in not a few of the reported cases a detached iliac thrombus was already present before operation, particularly in cases of thrombosis which had extended upwards into the femoral vein. It is also conceivable that no femoral thrombus exists in some cases and that a free iliac thrombus may be derived from as low a level as the popliteal vein. Because of the importance of the subject all the cases of free iliac thrombosis I have encountered will now be described. The technical aspects will be set forth in the section dealing with the operative treatment of femoroiliac thrombosis.

In a *second*, early fatal, case, the iliac vein was not explored. The findings at autopsy are noteworthy.

A woman, aged 55 years, whose blood pressure was 210 systolic and 140 diastolic, was subjected to a plastic operation on the gynecological service. On the twelfth post-operative day there was a sudden episode of dyspnea and substernal pain. Tenderness was elicited along the course of the left femoral vein but other evidence appeared to warrant the diagnosis of a coronary lesion and the patient was transferred to the medical service where she was under treatment for three weeks. During this period there were several attacks of dyspnea, thoracic distress, mild cyanosis, and sweating. Films of the chest were negative for infarction. A severe episode of oppression in the chest and cyanosis, accompanied by a sharp drop in blood pressure, occurred one month after operation. There were no signs or symptoms of thrombosis in the legs. Bilateral venograms were performed. That on the left revealed complete block of the femoral vein. At operation on the left femoral vein a partly organized and partly unorganized femoroiliac thrombus was removed. This was followed by free bleeding. On the following day another episode of pulmonary embolization led to ligation of the right femoral vein (no abnormality was found at the site of severance, because of the possibility of additional emboli being derived from this source). There was continuing dyspnea and cyanosis; the patient died 5 days after ligation of the femoral vein. At autopsy death was attributed to right heart failure due to a massive pulmonary embolus. The embolus was believed to have been lodged in the pulmonary artery for several days because it was adherent. There was a fragment of organized thrombus adherent to the wall of the left external iliac vein several centimeters above the ligature on the left femoral vein.

It seems fair to assume that the foregoing was a case of femoroiliac thrombosis with an additional iliac thrombus which became adherent in part, the free portion escaping to become lodged in the pulmonary artery. The ample bleeding from the cut end of the left femoral vein at operation was regarded as clear evidence of the absence of a substantial iliac thrombus or rather as the sign of a free venous pathway and therefore of the absence of an iliac thrombus of large size. That that assumption may be incorrect has already been stated and is disproven by the following cases.

A *third case* which was reported amongst the instances of thrombosis in ambulant individuals is briefly referred to here. It represents the only instance I have seen of bilateral free iliac thrombi of such size that each would have been lethal, or almost so, if it had reached the vena cava and pulmonary artery.

A middle aged man was standing before a mirror shaving when suddenly he collapsed. The diagnosis of pulmonary embolism became evident when thrombosis in the right leg appeared. Operation was performed a few weeks later when the thrombosis was noted to have extended into the femoral vein. At operation the thrombus, partly organized, reached to the beginning of the external iliac vein. The removal of the upper end was followed by bleeding from the external iliac vein in amounts sufficient to establish patency of the venous pathway. However, fine clips were placed on the cut end of the common femoral vein which was held open with suitable retractors, and suction was applied within the lumen of the external iliac vein. There was then indistinctly seen the lower end of a thrombus about an inch above the cut end of the femoral vein. This was grasped and a 3½-inch thrombus, ½ inch in diameter, lying free in the iliac venous system, was removed. Bleeding was now somewhat more profuse. The femoral vein was ligated and heparin was administered. Despite heparin (or perhaps because of too small dosage) a propagating thrombus in the left leg developed. When there was evidence of its extension into the femoral vein, operation was performed. The lesion was almost identical with that on the right side except that the thrombus in the femoral vein was more organized, suggesting that it had developed silently at about the same time as the one in the right leg. As on the right side there was a free iliac thrombus which was extremely large and fleshy and must have extended to, or almost to, the inferior vena cava.

In the *fourth case*, also reported elsewhere for other reasons, there was the escape of a free iliac thrombus without the use of suction.

Bilateral femoral thrombosis was present in this patient (Mount Sinai Hospital No. 515689), who had suffered several episodes of pulmonary embolization and in whom the signs of venous thrombosis had subsided by the time she came to operation. On the left side there was thrombosis of the superficial femoral vein and a free thrombus in that vein as well. On the right side the femoral thrombus extended to within a short distance of the inguinal ligament. There was no thrombus at the site of severance of the common femoral vein at this level. When, however, the upper ligature was removed in order to explore the external iliac vein for an additional thrombus, there escaped with a free flow of blood a substantial iliac thrombus. It should be noted that this patient had suffered a number of episodes of severe pulmonary embolization in the period of subsidence of clinical evidence of venous thrombosis in the legs and one can therefore assume that such episodes may have been due to other free iliac thrombi which escaped into the vena cava.

The *fifth case* (Mount Sinai Hospital No. 501934) is an excellent illustration of the necessity for the search for an iliac thrombus on the side of known femoral thrombosis rather than the ligation of the femoral vein on the opposite side without further study.

The patient, 50 years of age, had been operated upon for varicose veins 2 weeks before admission, at another institution. At that time the right saphenous vein and branches were ligated. An episode of pulmonary embolization occurred shortly before admission to Mount Sinai Hospital with a confirmatory film of the chest on admission. A venogram established the existence of an extensive thrombosis of the right femoral vein. At operation the common femoral vein was severed between ligatures. At this level there was no thrombus. Heparin was administered. Three days after operation there began a series of pulmonary infarctions. A venogram of the left leg established the existence of a normal



pattern and thus excluded (almost certainly) the left leg as the source of the continued pulmonary embolization. Accordingly an exploration of the right external iliac vein was carried out ten days after the ligation of the common femoral vein. A partially organized free thrombus was found in the external iliac vein above (not in immediate proximity to) the ligation on the femoral vein. The segment of the external iliac vein was removed. There were no further episodes of pulmonary embolization.

*Sixth case.* A young woman two weeks after childbirth was being treated for an assumed pneumonic lesion (chill, fever, physical signs), when she complained of pain in the left leg. Examination revealed suggestive evidence of venous thrombosis extending into the thigh, and operation was performed. The common femoral vein appeared normal but contained a soft thrombus which terminated at the level of the inguinal ligament. Although there was moderate bleeding from the upper end of the severed femoral vein, the iliac vein was explored. It contained a free soft thick thrombus about 2½ inches long. Its upper end tapered off almost to a point indicating the probable site from which a thrombus had been detached. The course after operation was uneventful. The discussion of swelling of the leg after ligation of the femoral vein will be taken up elsewhere and the supposed advantages of ligation of the superficial femoral vein will be aired. In passing, however, it may be noted that there was no swelling of the leg one year after operation when this patient, a professional dancer, was seen for check-up.

*Seventh case.* A gynecologist had performed a hysterectomy on a middle aged woman 10 days before the onset of pain in the calf extending into the thigh within 24 hours. There were no symptoms referable to the chest. At operation there was a recent soft thrombus in the femoral vein. Because bleeding from the upper end was not sufficiently free, the external iliac vein was explored with the removal of a thick thrombus which was at least 3 inches long. This was followed by free bleeding; the subsequent course was uneventful. Obviously death (or a sublethal episode) might have ensued if this large thrombus had been overlooked.

*Eighth case.* There were two leads suggesting the possibility of an iliac thrombus in this case, one being the long duration of the thrombosis in the leg, the other an episode of pulmonary embolization. The patient, a physician, noted pain in the right leg August 18, following swimming. Tenderness and reduced function developed. The temperature rose to 103°F. on September 6, and was uninfluenced by penicillin administered over a period of ten days. On October 19 an episode of pulmonary embolization occurred. Operation was performed the next day at another institution, consisting of severance of the superficial femoral vein. A thrombus was noted at this level. On the following day the patient was transferred to Mount Sinai Hospital for further exploration of the femoral vein. The common femoral vein was exposed. The thrombus within it terminated a short distance above the profunda. It was inspected and found to be smooth and rounded. The next steps can be quoted from the operative notes: It could be assumed the rounded end of the thrombus in the common femoral vein represented the termination of the thrombotic process. However, I was not satisfied that a thrombus was not present at a higher level and removed the upper ligature on the common femoral vein. There was a rather free flow of blood, certainly none of the greatly reduced flow which one would anticipate from an occluding thrombus. A suction tube was inserted for a distance of about two inches and a small fragment of thrombus was withdrawn. With this as a lead, the tube was reinserted a second and again a third time to a higher level. There was then withdrawn a thrombus a half inch or more in diameter and at least three inches long. Its removal was followed by a free flow of blood. Judging by the length and position of the thrombus it must have been lodged in part in the inferior vena cava. Heparin was administered during operation and was perhaps responsible for a hematoma in the wound which delayed convalescence.

The *ninth case* to be reported is one of an elderly man already described among the group of ambulant patients with venous thrombosis. An episode of pulmonary embolization, characterized by faintness and weakness, was decidedly transient but was the lead to exploration of the external iliac vein. At operation a thrombus terminating in the upper



portion of the common femoral vein was encountered. The upper ligature on the femoral vein was removed. Free bleeding followed. Nevertheless a search was made for a free iliac thrombus. The search was rewarded by the disclosure and removal of a thick, fleshy thrombus fully  $3\frac{1}{2}$  inches long. The post-operative course was uneventful.

*Venous thrombosis in transition to thrombophlebitis.* At the onset there should be a clear statement of the well-established fact that venous thrombosis is a distinctive lesion of the deep veins of the calf, often attended by upward propagation into the femoral vein or higher. Characteristically the propagated portion floats free in the femoral vein, the point of attachment being in one of the deep veins of the calf. Thus the term "deep venous thrombosis," which I prefer, appears to be an excellent one because it emphasizes the contrast between the lesion of the deep venous system and thrombophlebitis, in which the lesion usually is encountered in the superficial venous system. It is the saphenous veins and their tributaries which are involved ordinarily in the inflammatory process termed thrombophlebitis and not the deep veins of the calf. A differentiation between thrombosis and thrombophlebitis of the deep veins as emphasized by many writers has not only led to confusion but also to misunderstanding of the nature of the process and the indications for treatment. Concerning the latter we may assume that the diagnosis of thrombophlebitis of the femoral vein would be made by those who advocate the differentiation on the basis of pain, fever, tenderness and infiltration or the palpation of a firm structure along the course of the femoral vein. Accordingly pulmonary embolization would not be anticipated and conservative treatment would be advocated under such circumstances. That neither the diagnosis of thrombophlebitis nor conservative treatment may be justified under such circumstances will be proven shortly by illustrative cases. One author reports an 8 per cent mortality from pulmonary embolism in cases diagnosed clinically as thrombophlebitis. In other words the diagnosis of thrombophlebitis of the deep venous system must be difficult to make, the margin of error must be great, the incidence must be rare, and those who use the term should support its use by citing the features and presenting illustrative cases.

Another point to be made is that those who speak and write of the difference between thrombosis and thrombophlebitis in the deep veins (femoral) should prove that there is in fact a lesion of the deep venous system which begins as a thrombophlebitis in the same manner as inflammatory lesions of the superficial venous system are known to begin. As far as can be discerned from the literature, involvement of the deep venous system extending into the femoral vein is initiated only as a bland thrombosis. When thrombophlebitis is grafted on thrombosis it is of a distinctive nature (as will be shown) and different from thrombophlebitis of the superficial venous system. The fate of deep venous thrombosis, uninfluenced by therapy, varies. It is undoubtedly a self-limited condition in the preponderance of cases, and often pursues a silent or virtually silent course. In a relatively small proportion of cases there are clinical manifestations of pulmonary embolization. Although protracted cases are seen, the course of venous thrombosis may be regarded as essentially acute. There is however an important group of cases in which organization and adherence of the

thrombus occurs and chronic changes take place in the wall of the vein. This lesion is a distinctive one which may follow in the train of so-called conservative treatment. The results of this peculiar form of thrombophlebitis of the deep venous system are infiltrative edema of the leg, ulceration which so often is termed "varicose" and the other manifestations of venous stasis and lymphatic blockage. Evidence of bacterial infection is lacking.

In addition to the foregoing chronic variety of venous thrombosis there are a number of variants which I have encountered in the acute or subacute stage which appear worthy of note. Such variants are unusual in my experience but comparison with that of others cannot be made because the literature contains scarcely any reference to atypical forms of venous thrombosis. Usually these lesions cannot be recognized until exposed at operation. Almost all the atypical cases which have come under personal observation were complicated by pulmonary embolism yet not a few approached the picture of thrombophlebitis. Atypical acute and subacute venous thrombosis with features suggesting thrombophlebitis at times fall into three groups, according to personal experience.

*The first group* is that which is characterized by recession of symptoms to such an extent that the fact that a venous thrombosis may have been present is apt to be lost sight of at the time of an episode of pulmonary embolism. In these cases there appears to be a recession of thrombosis in the calf (or recession in manifestations) while it progresses silently in the popliteal and femoral veins or beyond. Fortunately rare, this is a decidedly dangerous form because the episode of pulmonary embolization is prone to be massive and potentially fatal. Thus, in a recent case not personally observed, the patient after a simple surgical procedure developed signs of venous thrombosis in the left calf several days after operation. The signs soon subsided. The patient was up and about, ready to go home, when a rapidly fatal episode of pulmonary embolism supervened. At autopsy there were thrombi in the iliac and femoral veins. Death was due to an occluding embolus of the pulmonary artery.

The insidious course is to be noted in the following case, described elsewhere for other reasons, which will serve here as an excellent illustration of the type in question.

The patient (Mount Sinai Hospital, No. 515689) was admitted on November 30, 1943. At that time the symptoms (at any rate in retrospect) were referable to a pulmonary embolus. Bilateral calf pain was complained of and subsequently there was the evidence of what appeared to be a mild bilateral venous thrombosis. The patient was discharged symptom free on January 4, 1944. She returned on January 21 with another episode of severe pulmonary embolization. There was no evidence of venous thrombosis in either leg. For this reason there was grave doubt that such a lesion existed, particularly because only large thrombi (from the femoral or iliac veins) could produce the severe episodes of pulmonary embolism. Bilateral venography revealed blockage of both femoral veins, which was found at operation to be due to thrombosis of both femoral veins. It is interesting to note that, in addition, there were free thrombi, partly organized, on both sides, and these would undoubtedly have led to further embolization. The patient recovered without any more episodes of pulmonary embolization.

*The second group* contrasts with the former and is generally known as one in which upward propagation of the thrombus is thought to be very rapid. There is considerable doubt in my mind as to the likelihood of extraordinarily quick extension of thrombosis from calf to groin, within 24 hours for example. More readily conceivable is the picture of a slower, silent, upward propagation with symptoms and signs appearing in the thigh soon after those in the calf because of reaction in the wall of the vein. The apparent, rather than actual, rapid propagation is proven in some of the cases (as in illustrative instances to be cited) when at operation soon after initial pain in the upper thigh there is encountered either a partly organized thrombus (proving its prolonged stay in the femoral vein) or a thrombus which has already extended upwards far beyond the limits of the femoral vein. In any event these cases of rapid spread of pain from the calf to the groin are to be recognized as urgent for active therapy because of the imminence of pulmonary embolism if it has not already occurred, and some of the cases fall decidedly into the category in which the diagnosis of thrombophlebitis may be made.

The first illustrative case is chosen as representative of the march of events under "conservative" therapy.

A 41 year old woman (Mount Sinai Hospital No. 503803) had an uneventful course after a hysterectomy for fibroids. On the fifth post-operative day there was pain and swelling in the right calf. Within 48 hours there was pain, tenderness and infiltration in the right groin, and 2 days later there were severe thoracic pain and dyspnea. At operation performed shortly after the episode of pulmonary embolism there was soft thrombotic material in the femoral vein which extended continuously up into the iliac for a length of six inches (presumably into the vena cava). The cap of the thrombus was more nearly organized than the rest and one may assume that the thrombus antedated the onset of pain in the thigh. The course was uneventful after removal of the thrombus.

The speed of propagation can only be surmised in the following case because a thrombus was found in the femoral vein the day the first symptoms in the calf appeared and before there were symptoms referable to the femoral vein.

A man 59 years old (Mount Sinai Hospital No. 516741) was operated upon under local anesthesia for hernia. On the tenth post-operative day there was the first complaint of pain in the left calf which was found to be infiltrated and tender. Operation was immediately performed. The femoral vein appeared normal and was severed between ligatures. However it was found to contain a recent thrombus. The upper ligature was removed and the upper end of the thrombus, which reached into the external iliac vein two inches above the inguinal ligament, was removed. The further course was uneventful.

In the following case of S. M. (Mount Sinai Hospital No. 516116), female, aged 23 years, a span of 24 hours covered the time of extension of pain and tenderness from the calf to the thigh, and yet at operation a partly organized thrombus had already extended to or into the vena cava. An exploratory laparotomy had been performed on this young woman for an abdominal mass which proved to be a retroperitoneal sarcoma. Radiotherapy was begun promptly after operation (with reduction in the size of the mass). On the 11th post-operative day there were pain and tenderness in the left calf followed the next day by tenderness in the femoral region. At operation the thickened femoral vein was filled with thrombus which was in part well organized and of yellowish color, in part composed of recent clots.

The thrombus of this mixed nature extended upwards 8 inches from the inguinal ligament. Its removal was followed by free bleeding. The post-operative course was uneventful in so far as the venous thrombosis was concerned.

*The third group* is that of acute and subacute thrombophlebitis. As already stated, cases of this variety are uncommon, only 3 having been encountered in a considerable personal experience. The peculiar features are to be seen best in the case reports, although cases observed by others may present other features. The difference between these cases and those of acute thrombophlebitis of the superficial venous system is obvious.

In the *first case* there was a striking contrast between the clinical evidence of thrombophlebitis and the obviously inflamed femoral vein on the one hand, and the contained soft and apparently recent thrombus on the other hand. The patient, male, 29 years old (Mt. Sinai Hospital No. 504776) was discharged convalescent after treatment for a virus pneumonia. He returned in 2 weeks with this history: three days after discharge there was an attack of palpitation and acute left thoracic pain of two hours' duration. Two days later pain in the left calf appeared and one week later pain in the left inguinal region. The leg and thigh became greatly swollen and tender. For a week before admission there were chilly sensations and fever. There was an episode of right thoracic pain shortly before admission. On admission, fever, the obvious swelling of the leg, tenderness and thickening along the course of the femoral vein, and tender, enlarged femoral lymph nodes established the diagnosis of thrombophlebitis. Nevertheless, the episodes of pulmonary embolism led to operation. The femoral vein, intimately adherent to the artery, presented a bluish-white wall. The assumption that the contents would be organized adherent thrombus proved to be incorrect, for the thrombus consisted of bluish-black blood clot which was of more jelly-like consistency in the iliac vein. The cap, which may have been situated in the vena cava, presented the smooth appearance of a platelet thrombus. The post-operative course was uneventful except for the appearance of signs of thrombosis in the right calf which subsided soon after the ligation of the right femoral vein.

The *second case* (Mount Sinai Hospital No. 503672) was that of a patient admitted April 3 (the date should be noted) with the history of a fracture of the left ankle treated by immobilization in plaster and a recurrent attack of left renal colic directly before admission. Removal of a ureteral stone was carried out on April 6. On April 9 there occurred an attack of substernal pain, dyspnea, weakness, and sweating. There was no evidence of venous thrombosis; coronary insufficiency could not be proven. The patient was not well for the next month, one of the features being persistent slight cyanosis. The left kidney was explored for a stone known to be present, on April 30. On May 10 there was an episode similar to that of April 9, and now identified as one of pulmonary embolism. Obvious inflammation of the left femoral vein was then noted with tenderness and thickening along its course. At operation the internal saphenous as well as the common femoral vein were occluded by organized thrombi. That in the femoral vein was greyish-red, soft, friable and adherent. It was extracted from the iliac vein, the removal of a brown-red cap being followed by a free flow of blood. There was no recurrence of pulmonary embolism after operation.

The *third case* (Mount Sinai Hospital No. 502345) was an outspoken one of bilateral thrombophlebitis in which the organized thrombus which existed on both sides was capped by soft and more or less free thrombotic material. The potentialities for pulmonary embolism were obvious. This 53 year old man was admitted and operated upon for an acute putrid pulmonary abscess of three weeks' duration. One month later, when the pulmonary status was entirely satisfactory, fever, which had never subsided, reached a higher level and pain in the left groin appeared. Two days later pain in the right inguinal region was complained of and there was some tenderness along the course of both femoral vessels as

well as in both calves. Venograms revealed surprisingly advanced blockage of both femoral veins. The operative findings were similar on both sides, the lesion being more advanced on the left. The operative field in each case was occupied by edematous connective tissue and many succulent lymph nodes. The femoral sheath was whitish and thickened. The thickened whitish femoral vein contained putty-like adherent thrombotic material. This was capped, in the iliac vein, by free currant jelly-like thrombi. The post-operative course was characterized by gradual recession of fever and of swelling of the legs.

The microscopic examination of excised segments of the femoral veins was of great interest. The vein itself revealed pronounced cellular infiltration, consisting of polymorphonuclear and round cells. The thrombi were composed of large numbers of polynuclear cells in addition to the other cellular elements of the blood. No bacteria were to be seen in sections stained for the purpose, although it may be said in passing that in another similar case in which cultures were taken of the thrombus at the time of operation, *Staphylococcus albus* B. was grown.

The discussion of atypical forms of venous thrombosis may be closed by a brief reference to two extreme varieties. One is a truly chronic form in which one or both legs are the seat of an organizing adherent thrombus in a thick-walled vein. It is of great interest to note that even in such cases recurrent pulmonary embolism may take place as in the case of a female physician who had been suffering for several months both from chronic thrombosis of the femoral veins and episodes of pulmonary embolism. The course had been uninfluenced by the administration of heparin, perhaps because of small dosage. The other significant feature was the existence of a soft free cap-like thrombus surmounting the upper end of the organized thrombus in the thickened iliac vein. This explained the recurrent pulmonary embolism before operation and its removal the non-occurrence after operation.

The other variety, extremely rare in my experience, is the conversion of a bland venous thrombosis into a suppurative phlebitis. Special factors appear to be responsible for this change as in the case of a patient operated upon for an extensive colonic cancer who developed venous thrombosis in the left leg after operation. This subsided in large part without specific therapy. Operation was then required for a putrid pulmonary abscess which may have been of post-operative (aspiration) origin or the result of infection of an infarct. With a considerable deterioration of the general condition there now appeared evidence of inflammation in the pathway of the main veins of the leg and thigh. At operation pus was found in and about the popliteal, femoral, and iliac veins, with scarcely any remnants of antecedent thrombi.



## DOCTOR I. C. RUBIN ANNIVERSARY VOLUME PRESENTATION

*On October 24, 1947, Doctor I. C. Rubin was presented with a special issue of the Journal of The Mount Sinai Hospital, dedicated to him by his colleagues, associates and friends, on the occasion of the twenty-fifth anniversary of the Rubin Test and to mark the completion of over forty years of his association with The Mount Sinai Hospital.*

*Prominent men in medicine, former associates and pupils, hosts of friends and grateful patients came to do honor to Doctor Rubin. The meeting, held at the Blumenthal Auditorium, was opened by Mr. George B. Bernheim, the President of The Mount Sinai Hospital. On introducing the speakers of the event, he made a few brief remarks which though serious in thought were expressed in a most amusing manner. Those who followed him, as will be seen from the following transcripts, paid high tribute to the humane qualities and the great skill of Dr. Rubin as well as to the remarkable contributions he has made in the field of Gynecology. Doctor Rubin's reply brought to a close the meeting which was marked by unusual warmth and sincerity.*

*Dr. George W. Kosmak:* We are gathered here today to commemorate a memorable occasion, namely, the introduction into medical practice of a procedure which has revolutionized the diagnosis and treatment of a previously baffling condition. And in doing so we must give due credit and praise to a noted member of the Mt. Sinai Hospital staff, a man who not only originated the procedure, but continued to further develop and make of its application an almost routine and accepted procedure. For the introduction of tubal insufflation in our medical armamentarium spells a great scientific advance, it means probably as much to the doctor as it does to the patient.

The ability of women to bear children successfully constitutes an important factor in the welfare and happiness of mankind. When sterility seizes upon a nation, it is a destructive force. Growth in peoples as in all other forms of life is of signal and primary importance. Unfortunately there are many factors which militate against a normal increase or even a balancing of populations. Wars take their toll, likewise starvation and disease. Some of these may be overcome by evident means but they demand great and widespread efforts, they are costly and time consuming. But aside from these, in seeking out the causes for sterility in women, it became evident that they must be separated into two great classes, those of a general or constitutional character and those dealing with the individual organs concerned. The latter, especially, have constituted a problem of world wide interest for many years. Leaving out the palpable causes, there remained a group of women in whom no satisfactory reason could be elicited although an obstruction to the passage of the ovum from its productive origin to the site of its further development seemed the most reasonable. But how to detect it remained a problem. The involved structures are delicate in their make-up, efforts to determine whether the passages were obstructed necessitated often major operative procedures or injection into the uterus and tubes of substances which would render them visible to the x-ray. There were risks and disadvantages evident to the medical as well as the lay mind. It was at this time that the thought occurred to Dr. Rubin that the passage of gas through the tubes would disclose whether these were at fault as an obstructive agent. He put this thought into effect at this Hospital on a memorable day, November 3, 1919, when he did his first insufflation test on a woman who soon demonstrated its success by becoming pregnant within two months and giving birth subsequently to a full term child.

This patient, Mrs. R. B., was the counterpart in a sense of Jane Crawford, upon whom Ephraim McDowell did the first successful operation for an ovarian tumor in 1809. Courage was essential in both instances, on the part of the doctor as well as the patient, notwith-

standing the difference in time, in surroundings, in knowledge. In both of these pioneers in their profession, as well as many others who contributed to advances in medicine, it was the courage of personal convictions which stimulated these men to do great-deeds.

Dr. Rubin was not content to rest upon his laurels, he continued his studies and many others have developed further his original thesis. The vast field which was opened up is amply demonstrated in the classical text-book on the subject which has recently been published. I feel a personal pride in this work for I urged Dr. Rubin to bring it out. His book on "Uterotubal Insufflation" is a classic in American medical literature and will serve as an authoritative expression of the accomplishments in this special branch of medicine. It will constitute a monument to the conscientious efforts of an outstanding clinician and research worker of which this Hospital and the profession of medicine may well be proud.

His medical colleagues have evidenced their interest and appreciation of Dr. Rubin's accomplishment by presenting to him a memorial volume which is more than a mere aggregation of pages of scientific articles, it is an acknowledgement of their faith and regard in a fellow worker. I feel it a personal honor to have been asked to serve as the chairman of the committee for this special volume, although my own contribution to its production is a minor one as compared to the laborious work and effort which has been expended upon the same by Dr. Joseph Globus to whom all praise and credit is due.

*Mrs Roger W. Straus:* It is a very real pleasure for me to be here and because of my deep regard and admiration for Dr. Rubin, I was most happy to have been asked to take part in this ceremony today.

I think that Dr. Rubin has contributed more to the fundamental happiness of thousands of women the world over than any other person I have ever heard of. Unfortunately, I did not know Dr. Rubin at the time when my children were born—he is too young and I am too old—but in these years that I have known him, I have often thought what great comfort and solace he must have been to the hundreds of women with whom he has come in personal contact because of his great gift for understanding, kindness, and sympathy. And so, Dr. Rubin, I did not come here today to congratulate you but to congratulate Mount Sinai Hospital for the many years that she has had the privilege of having you so closely associated with her.

*Dr. Brooke M. Anspach (Philadelphia):* The physician who loves his profession tries not only to perfect himself in the practice of the art but also to make some contribution to its advancement.

He believes, of course, that the conclusions he draws from his efforts as he goes along are entirely sound but he is bound to find that experience and time must be awaited to estimate their worth correctly.

Medical journals are filled with writings that sooner or later become a disappointment to their authors. What appears to be a truth becomes a cast-off fallacy; the dictum of today is lost in the judgment of tomorrow; 'til time runs out there can be no final settlement; we never reach the end; we are always striving for more.

All we may say is that the path of progress in science is strewn with the wrecks of false assumptions. We review the past, we become aware of the present, we speculate upon the future.

As we look in retrospect upon the last fifty years in the practice of medicine we marvel at the changes brought about, at the knowledge that has been acquired; we recall lives lost that nowadays would be saved.

It is the sum of the constant efforts of a host of workers to unravel the mysteries of life and disease; for most of us there is only the satisfaction of having tried; to many there is credit for facts that have endured.

It falls to the lot of only a few to make a definite addition to the practice of medicine; Dr. Rubin is one of them; he saw the light and gave a new thing to the science and art of gynecology.

What hearts desire of womankind exceeds the fond hope of motherhood! Years ago we could only say to the sterile woman that an exploratory incision was needed to find out whether her tubes were open or closed.

Dr. Rubin answered the riddle; he created the idea of uterotubal insufflation. Like many other inventions it seemed a simple matter after it was done—an idea that might have occurred to many others—but as a matter of fact it never did because the thinking ahead, the spark of originality was missing.

Dr. Rubin did not rest content with merely solving the problem. Clever and original as he is, with the collaboration of interested gynecologists all over the world the essence of his test has been a path along unblazed trails to correlated studies. All of this with kymography and hysterosalpinography has enabled us to reach a long sought object.

The condition of the Fallopian tubes, to say nothing of other factors in the sterile mating, may be determined now with certainty. The entire subject is admirably presented in Dr. Rubin's recent book.

We gather here therefore to do this man honor, to felicitate him. We appreciate and share the satisfaction he must feel at his accomplishment. Paraphrasing Joseph Addison he has done more than merely to command success, he has deserved it.

*Mr. Charles A. Riegelman:* I am very happy to be here and particularly happy to be permitted to join this audience in paying tribute to Dr. I. C. Rubin, who has been my friend for upwards of 35 years.

Dr. Rubin is a rare person indeed, combining, as he does, with his scientific, scholarly and professional attainments, great sweetness, fine character and unusual capacity for loyal friendships. I am glad for the opportunity of saying this to him in your presence. In behalf of this audience, as well as in behalf of his numerous other friends, not here present, I wish to express our hopes for many more years of happy and contented existence and continued usefulness to the community.

*Dr. Eli Moschowitz\*:* There is no need to review the several significant steps in the progress of the discovery of Dr. Rubin, from the visualization of the Fallopian tubes with various radio-opaque substances to oxygen insufflation, then to carbon dioxide and finally to the addition of the kymograph which converted this technique into one of the most refined instruments of precision of medical science. Each step represented a technical advance, and most observers would have been content to stop somewhere in the midjourney toward the desired goal. But with the doubt of the scientist and sensitive perception of the artist, Dr. Rubin aimed at nothing less than perfection. Finally after five years of experimental checking and rechecking, the method appeared safe, and with considerable trepidation, was tried in the living woman on November 3, 1919, a date that deserves remembrance in the annals of gynecology.

Visualization of the Fallopian tubes with radio-opaque substances had been done by a number of observers previously. These attempts have been frankly acknowledged by Dr. Rubin in many of his publications, although they were unknown to him when the idea was born in his own mind. The difference between Dr. Rubin and these observers was that he possessed that mental attribute so vital in the pursuit of discovery, namely the follow through. The first radical departure that distinguishes Dr. Rubin's labors from those that preceded him was the use of a gas for tubal insufflation and he has pursued the potentialities of this procedure ever since.

A follow through in meditation is as essential in science as in a stroke in tennis. This indeed is the mental quality that distinguishes scientists of distinction from lesser lights. It is altogether probable that many of the scattered observations that clutter medical writings could be integrated into fundamental laws of medical science by this discipline.

\*This tribute was published in the anniversary volume.

Had Dr. Rubin merely perfected the insufflation apparatus, the achievement would have been considerable. But again he followed through and he determined not only its clinical applications in relation to sterility but opened the hitherto comparatively unexplored field of normal and abnormal tubal function. He also discovered some therapeutic potentialities of tubal insufflation, but these still await complete fulfillment. Dr. Rubin therefore deserves acclaim not only because he discovered a precision technique, but particularly because his labors have been so thorough that little of any consequence has been added by others. This is not the usual history of technical discoveries in science. For the present and probably for the immediate future, Dr. Rubin's observations stand unchallenged.

Even had he not discovered tubal insufflation, Dr. Rubin would have achieved distinction for his other contributions in his chosen field. Since 1910 Dr. Rubin has written two books, one on Symptoms in Gynecology; Etiology and Interpretation, and one on Uterotubal Insufflation, and 88 articles. In addition, he has contributed the chapters on sterility in the Curtis system of Gynecology, in the system of Surgery edited by Dean Lewis, and the chapter on uterotubal insufflation in the Cyclopedia of Medicine published by F. A. Davis and Co. Of the 88 articles, 33 are devoted to visualization of the Fallopian tubes and uterotubal insufflation. The remaining 55 reveal an unusual versatility. Dr. Rubin has delved into almost every field of gynecology; clinical, operative, diagnostic, physiological and morbid anatomical. His contributions are substantial and while of a lesser magnitude than those devoted to uterotubal insufflation, they reveal the sound thinker, the keen observer, the student, the critic, the teacher, and the humanitarian. There is not the slightest tinge of propaganda in any of Dr. Rubin's papers nor is he ever a mere encyclopedist. There is a personal touch in all of Dr. Rubin's writings; they are never stereotyped, and the reader can always carry away something new and informative.

It is given to few in our calling to make a first rate discovery and above all to achieve recognition for it during his lifetime. This satisfaction is not only Dr. Rubin's but our own since medical science is richer for his labors and he has endowed gynecology with a method that has appreciably widened its scope. In the essays by his colleagues that follow we are only trying to return to Dr. Rubin what he has given us. They represent but a small compensation for the rich endowment he has conferred, but in all events they serve as a token of our gratitude and admiration.

*Dr. Seymour Wimpfheimer:* I am here to express the sentiments of the younger men, who have come under the guidance and influence of Dr. Rubin. It was a great opportunity to be taught by him and profit by his teachings.

To this expression of appreciation, I would like to add my own personal thanks and tribute to Dr. Rubin, the teacher with great wealth in original thought; the student, who is always eager to learn new concepts and subject them to a thorough test; the investigator, who finds pleasure and joy in research; the lecturer, whose talents have been sought far and wide in all parts of the world and were rewarded by many honors in as many countries; and the friend of the younger men, always ready to help them at the outset of their career and guide them through the period of uncertainty.

We are all deeply grateful to him and hope that our happy association will continue for many years to come.

*Dr. I. C. Rubin:* One cannot listen to friends speaking in such generous terms of praise and approval without being deeply moved to a sense of gratitude and appreciation, and so I want to thank you all for being so kind to me. I want especially to thank Dr. Kosmak, Dr. Globus, Dr. Baehr and Mr. Riegelman and members of their committees for having conspired against me in such benevolent and kindly fashion. I should like to thank all friends here assembled for taking time out from busy schedules to participate in this meeting. I feel deeply obligated to you all for this fine gesture of friendship.

For many years I have held the private opinion that the time to give public recognition

to an individual for meritorious work and character is during his lifetime when he may hear what is said about him, about his life, his aims, his work, difficulties, struggles, minor or major triumphs and disappointments, so that he might profit by the assessment, correct his shortcomings and eventually be able to indicate what he would like to have recorded in self-memorial. I am not so sure that I can subscribe to this belief now, being placed in the very position I might have advocated for others. Nevertheless, I must confess that it is agreeable to be able to stand before you and not to have to take it lying down!

Somehow, at this moment, there keeps humming in my ears the famous couplet of Cowper's "Knowledge is proud that he has learned so much; wisdom is humble that he knows no more." There is a remarkably chastening and deflationary quality in those lines that is good for the soul. For working up a sense of overdue humility, I can recommend to anyone, far worthier than myself, to be the recipient of an anniversary volume. He would emerge, if not a better man, surely a much humbler one. And so in all humility, may I say to you, all my friends, associates, and colleagues that I shall cherish this unforgettable lovely hour spent together. May I take this occasion to thank the generous sponsors of and contributors to this anniversary volume which I shall treasure. It is truly a labor of love to which so many distinguished colleagues from near and far have given of their thought, their time and effort toward the furtherance of scientific knowledge. I look forward with much eagerness to reading this book. It will serve as a constant reminder of their good fellowship. Its perusal will surely prove to be a thrilling adventure which I can only hope all of you who may read it will share with me.

In closing, I should like to express my appreciation to the trustees of Mount Sinai for providing the facilities of this great hospital which made my work possible. This is a fitting occasion also to acknowledge my personal debt to teachers and predecessors, one of whom, Dr. Robert T. Frank, I am happy to see in our midst; as well as members of my staff for their wholehearted cooperation and confidence. To the nurses I extend my affectionate greetings. Mount Sinai has a long and distinguished record of achievement. During its well nigh century of existence it has occupied an important place in the community and the nation, succoring the sick and advancing the art and science of medicine. Let us hope Mount Sinai Hospital will go on to its next century of service with the same energy and spirit that have characterized its progress in the past.

Thank you again from the bottom of my heart.



## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Reporting Industrial Dermatitis.* S. M. PECK. Compensation Med., 1: 3, March, 1946.

A new and more practical and complete form for reporting industrial dermatitis is given. The form is so arranged that if it is followed properly, nothing will be forgotten that might prove of aid in establishing a correct diagnosis. The reason for the inclusion for many of the questions in the form is discussed in detail. The importance of some of the questions especially in proving a case to be compensable or non-compensable is stressed.

*Metabolic Requirements of Gram-Negative Bacilli Determining Resistance to Penicillin.*

G. SHWARTZMAN. Federation Proc., 5: 1, March, 1946.

Amino acids affected significantly the action of penicillin upon Gram-negative bacilli. Dicarboxylmonoamino acids (i.e. aspartic, glutamic, hydroxyglutamic acids and asparagine), cystine and  $\alpha$ -amino acids with guanidine, glyoxaline and pyrrole nuclei, all possessing in common—NH grouping in the nucleus (i.e. arginine, histidine and hydroxyproline, respectively) were antagonistic to the action of penicillin. The anti-penicillin effect of these amino acids could be reversed by dl-methionine, the reversal being facilitated by methionine sulfoxide and threonine following a reciprocal quantitative relationship. When substances of mixed amino-acid composition (broth or casein hydrolysate) were used for cultivation, a mixture of methionine, methionine sulfoxide and threonine markedly enhanced the susceptibility of *Brucella*, *Eberthella*, *Escherichia*, *Salmonella* and *Shigella* to penicillin.

Modifications in resistance to penicillin could be induced in the absence of the drug by altering the metabolic requirements of *E. coli*. Following a number of serial passages in basal medium alone and in basal medium supplemented by amino acids antagonistic to penicillin, variants were obtained which differed markedly in resistance to penicillin. The changes were in inverse relation to concentration of antagonistic amino acids in the media used for the passages. The variants obtained from passages in basal medium alone apparently acquired the ability to synthesize penicillin-antagonists. They possessed the highest resistance to penicillin. Variants from cultures supplemented by antagonistic amino acids lost at least in part the ability for synthesis. They showed the highest susceptibility to penicillin. Furthermore, a variant was obtained which failed to grow in basal medium alone. It grew well when the medium was supplemented by leucine, hydroxyglutamic or aspartic acid. In basal medium containing leucine the susceptibility of the variant to penicillin was 9-12 times greater than in basal medium containing a dicarboxylmonoamino acid. It is suggestive that certain intermediate products of dicarboxylmonoamino acids may be responsible for the antagonism. The studies seem to indicate a relationship between the antibiotic activity of penicillin and the cellular metabolism of Gram-negative bacilli.

*Disorders of the Scalp.* H. T. BEHRMAN AND O. L. LEVIN. Merck Report., April, 1946.

This survey discusses various scalp conditions and their treatment. The diseases are discussed under the heading of infections (tinea capitis, favus, pediculosis), abnormal

types of hair and alopecia (congenital, localized and premature). It is emphasized in this report that many disorders of the scalp are amenable to therapy and should be treated accordingly.

*Changes in Sensory Adaptation Time and After-Sensation with Lesions of Parietal Lobe.*

M. B. BENDER. *Neurol. & Psychiat.*, 55: 299, April, 1946.

A patient with a gunshot wound of the left posterior parietal and occipital lobes showed disturbances in visual, cutaneous and proprioceptive senses on the right side of his body. These defects were elicited under special conditions. Whereas with single stimulation his vision appeared to be intact, simultaneous stimulation of his right and left fields of vision caused the image on his right to become extinct. This phenomenon of extinction was found in various forms, from fluctuation and blurring to complete invisibility of an image. A similar phenomenon was found for cutaneous perception. Besides this, the patient showed a reduction in the adaptation time for cutaneous and proprioceptive modalities. The latter was pronounced enough to produce a disorder in his body image. Another patient, with a gunshot wound in the left anterior parietal and posterior frontal lobes, showed motor and sensory disturbances in the right side of his body. The sensory changes could be elicited only under special conditions and were expressed as a prolongation of the periods of sensory adaptation and after-sensation. With paired equal stimulation, sensation was apparently enhanced on the affected side. With paired simultaneous stimulation in which a strong stimulus was applied to the left side and a weak stimulus to the right side, there was reduction of sensory adaptation time, and even extinction of sensation. This case thus illustrates the phenomena of "enhancement and extinction" of sensation, either of which could be obtained on stimulating the same area of the skin at different times and under different conditions. It is analogous to the experimental observations made by Dusser de Barenne and associates for motor function in the chimpanzee. These patients also showed decrease or increase in after-sensations. These observations reveal that most of the disturbances in these patients were due to normal mechanisms (such as rivalry with resultant dominance, sensory adaptation and after-sensations) which became apparent under pathologic conditions, such as lesions in the parietal lobe. Why these mechanisms become so apparent is not clear. Without the foregoing considerations and special investigations of sensations, most of the symptoms could not be explained, because routine neurologic examination for sensation revealed an essentially normal status in both these patients.

*Brain Tumor: Its Contribution to Neurology in the Remote and Recent Past.* J. H. GLOBUS.

J. Neuropath. & Exper. Neurol., 5: 85, April, 1946.

In an endeavor to assay future progress in neurology a review is presented of the contributions to this field by the advancing knowledge of brain tumor from the 18th century to the beginning of the 20th century. The earlier morphological descriptions of brain tumors by Morgagni and Abercrombie were particularly vivid and accurate. Walshe, Lambert, and Ladame's clinico-anatomical observations later led to the development of the modern concept of localization of function as initially enunciated by Broca, Bramwell, Horsley, Cushing, and Mills, among others, subsequently enriched this concept. The author has this to say regarding new diagnostic methods, "Increased mechanical facilities in diagnoses in recent years have led us to stray from the path upon which these older investigators brought us out of darkness to this age of relative neurologic enlightenment. Greater promise for lasting success in solving some urgent problems in neurology rests with the return to the road of thorough clinical study and anatomico-physiologic structure-function relationships."

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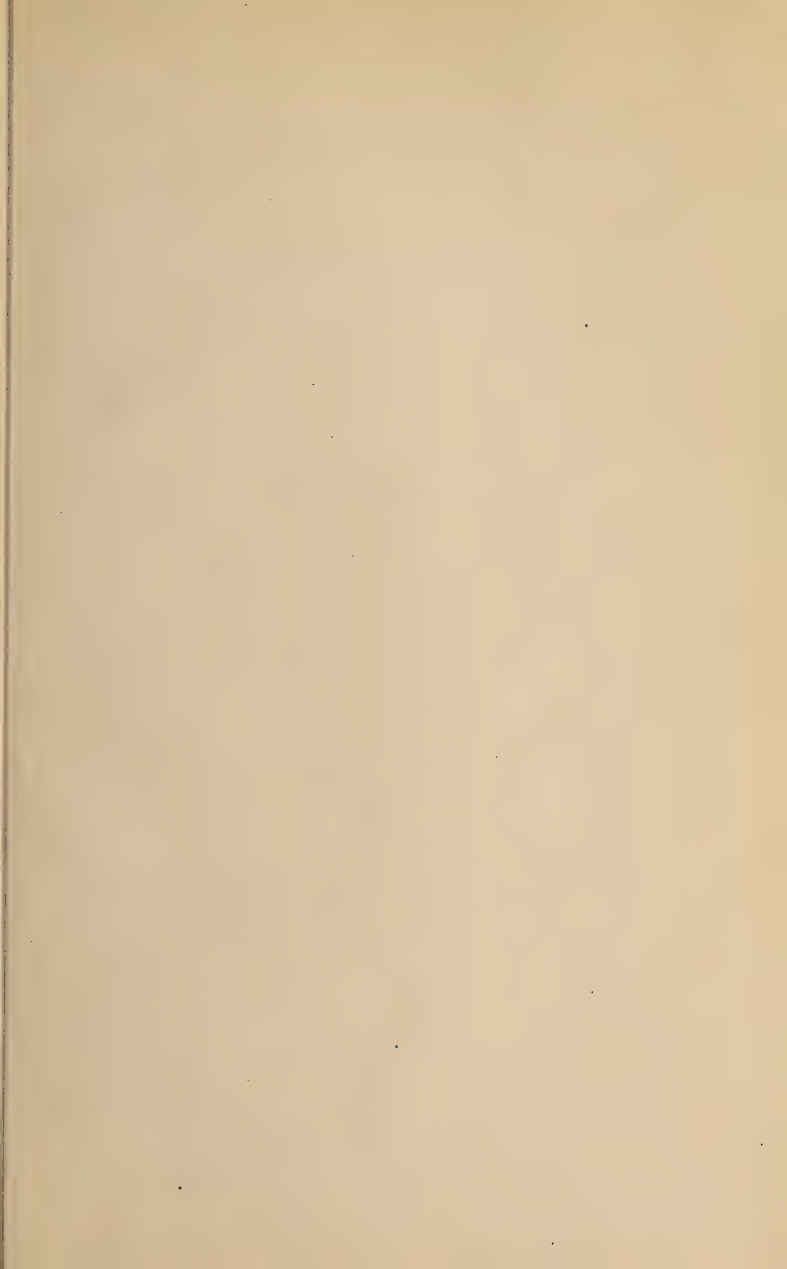
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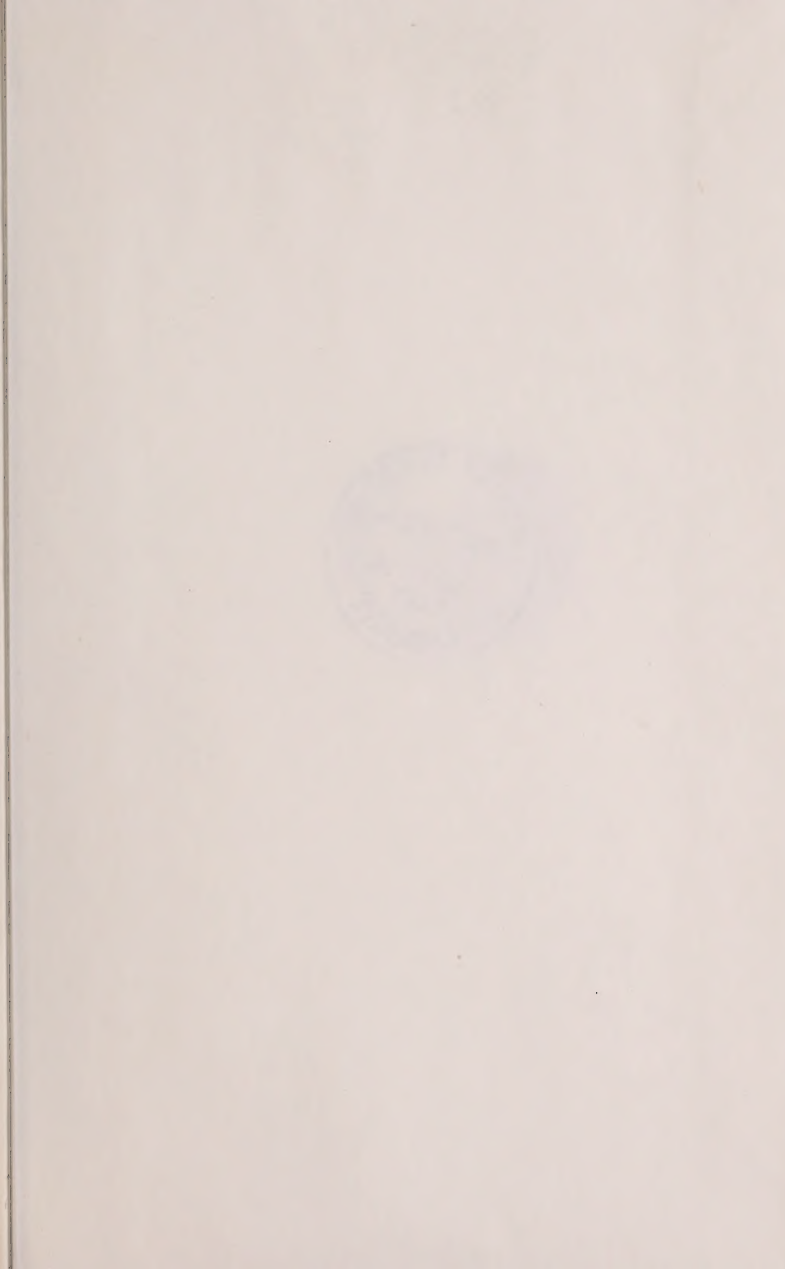
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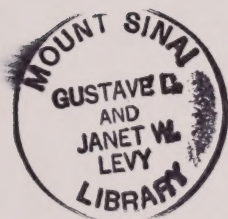




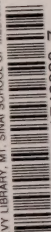








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